C A N A D A
PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000016-960

C O U R S U P É R I E U R E
Recours Collectifs

DOMINIQUE HONHON

Requérante

-c-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Intimés

-et-

ME MICHEL SAVONITTO, es-qualité de membre du Comité conjoint

REQUÉRANT

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A
PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000068-987

C O U R S U P É R I E U R E
Recours Collectifs

DAVID PAGE

Requérant

-c-

PROCUREUR GÉNÉRAL DU CANADA

PROCUREUR GÉNÉRAL DU QUÉBEC

SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Intimés

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

REQUÊTE POUR DIRECTIVES PRÉSENTÉE PAR LE MEMBRE DU COMITÉ CONJOINT AUX FINS DE RÉÉVALUER LES ASPECTS FINANCIERS DU FONDS
(Art. 10.01 (1) (i) (ii) de la Convention)

À L'HONORABLE JUGE EN CHEF FRANÇOIS ROLLAND, JUGE DÉSIGNÉ AUX FINS D'ENTENDRE LES DIVERSES REQUÊTES DANS LE PRÉSENT RECOURS COLLECTIF, LE REQUÉRANT EXPOSE RESPECTUEUSEMENT CE QUI SUIT :

INTRODUCTION

1. En novembre 1999, les tribunaux de la Colombie-Britannique, de l'Ontario et du Québec (ci-après collectivement désignés «Tribunaux») ont approuvé la Convention de règlement relative à l'Hépatite C 1986-1990 (ci-après désignée «Convention») entérinant ainsi une entente intervenue entre les diverses parties impliquées et permettant d'indemniser certaines personnes infectées par le virus de l'Hépatite C durant la période s'échelonnant entre le 1er janvier 1986 et le 1er juin 1990;

2. Conformément à la Convention, le Comité conjoint avait l'obligation de présenter, dans les 180 jours suivant le 31 décembre 2001 et par la suite, à tous les trois (3) ans, une requête devant les Tribunaux aux fins de réévaluer le caractère suffisant du point de vue financier du fonds en fiducie et, notamment, d'envisager la possibilité de supprimer certaines restrictions fixées initialement pour garantir sa suffisance;

HISTORIQUE

3. Le 17 juin 2002, le Comité conjoint présentait une première requête à cet effet recommandant à la Cour d'ordonner la suppression de la restriction prévue au paragraphe 4.01(1) b) exigeant le report du paiement de 5 000$, et ce, tant en vertu du Régime à l'intention des Transfusés infectés par le VHC, que du Régime à l'intention des Hémophiles infectés par le VHC («les Régimes»). Le Comité conjoint recommandait ainsi que chaque personne ayant le droit de recevoir un paiement reporté conformément à cet article obtienne, sur-le-champ, paiement de ce montant, majoré des intérêts au taux préférentiel à compter de la date du paiement de 15 000$ aux termes du paragraphe 4.01(1) b), le tout tel qu'il appert du dossier de la Cour;

4. Le 11 juillet 2002, cette Cour, après enquête et audition, rendait jugement et entérinait la recommandation du Comité conjoint en concluant que la suffisance du Fonds permettait que le paiement de la retenue de 5 000$ prévue à l'article 4.01(1) b) soit fait aux réclamants qui y avaient droit, et permettait dorénavant le paiement de l'indemnité de 20 000$ sans aucune retenue, le tout tel qu'il appert du dossier de la Cour;

5. Nonobstant la preuve présentée à la Cour en juin 2002 pour cette première réévaluation de la suffisance du Fonds, le Comité conjoint n'a pas jugé à propos de demander la levée des restrictions prévue aux articles 4.02 et 6.01 préférant reporter à une date ultérieure l'examen de ces deux restrictions aux fins de rassembler et réunir plus d'informations sur le nombre de personnes composant le Groupe;

6. Le 22 juin 2004, soit avant le terme de 3 ans prévu à la Convention, le Comité conjoint présentait ainsi une *Requête en réévaluation de l'entente relativement aux restrictions financières* et, selon les évaluations obtenues des actuaires, recommandait à cette Cour d'ordonner :

   a) la suppression de la restriction contenue aux articles 4.02(2) et 6.01(1) des Régimes qui restreint le montant d'indemnisation à 70% de la perte annuelle de revenu net, de façon à ce que telle perte soit indemnisée à 100%;

   b) que chaque membre visé se voit payer le montant correspondant au 30% non indemnisé, majoré des intérêts calculés à compter de la date de chaque paiement reçu relativement à la perte de revenu ou de soutien;

   c) que la restriction contenue à l'article 4.02 (2)(b)(i) des Régimes qui restreint à 75 000$ le montant de revenu brut admissible pour les fins du calcul de la perte annuelle de revenu net soit majorée à 300 000$; et

   d) que chaque personne ayant reçu une indemnisation inférieure à celle qu'elle aurait pu recevoir en vertu des articles 4.02(2), 6.01(1) et/ou 4.02(2)(b)(i) de l'un ou l'autre des Régimes avec une limite de 300 000$ de revenu brut au lieu de 75 000$ se voit payer un montant équivalant au manque à gagner, majoré des intérêts sur la différence, calculés à compter de la date de chaque paiement reçu relativement à la perte de revenu ou de soutien en vertu des articles 4.02(2) et 6.01(1) des Régimes;

   le tout tel qu'il appert au dossier de la Cour;

7. Le 7 juillet 2004, après enquête et audition, cette Cour accueillait ladite requête et entérinait les recommandations du Comité conjoint tel qu'il appert au dossier de la Cour;

8. Pour les fins de la préparation de la seconde réévaluation triennale (évaluation à la date du 31 décembre 2014) de la suffisance du Fonds, le Comité conjoint a requis une mise à jour des études médicales et actuarielles en plus de préparer lui-même un rapport d'analyse des données recueillies par l'administrateur contenant les hypothèses de travail transmises aux actuaires pour la préparation de leur évaluation;

9. Suite à la signification des expertises médicales et actuarielles et du rapport du Comité conjoint, le gouvernement a également déposé une expertise actuarielle;

10. Après avoir pris connaissance de l'ensemble de la preuve documentaire déposée et des plaidoiries écrites des procureurs, le tribunal rendait jugement le 6 mars 2007 et déclarait que le Fonds en fiducie était financièrement suffisant au 31 décembre 2004, tel qu'il appert au dossier de la Cour;

11. Par la suite, le 19 juillet 2007, le Comité conjoint présentait une *Requête en réévaluation de l'Entente relativement aux restrictions financières* concernant la levée de la dernière restriction contenue à l'article 4.02 (2) (b) (i) qui restreignait à 300 000 $ le montant de revenu brut admissible pour les fins du calcul de la perte annuelle de revenu;

12. En date du 17 janvier 2008, le tribunal rendait jugement et ordonnait la modification de cette dernière restriction en haussant le maximum admissible pour le calcul de revenu brut à 2 300 000$ et en prévoyant une approbation préalable particulière pour toute demande excédant 300 000$ devant être émise par le tribunal ayant juridiction sur le réclamant impliqué, le tout tel qu'il appert du dossier de la Cour;

13. La troisième révision triennale a débuté en 2008 afin d'évaluer si le fonds en fiducie était financièrement suffisant à la date d'évaluation du 31 décembre 2007, ce qui fut constaté et déclaré par la Cour dans son jugement rendu le 13 avril 2010;

14. La quatrième révision triennale qui a débuté en 2011 avait pour but d'évaluer si le fonds en fiducie était financièrement suffisant à la date d'évaluation du 31 décembre 2010 et la Cour a rendu jugement le 3 juillet 2013 en déclarant que le fonds en fiducie était suffisant à cette date d'évaluation, le tout tel qu'il appert du dossier de la Cour;

LE CONTEXTE ACTUEL :

15. Pour les fins de l'actuelle et cinquième révision triennale de la suffisance du fonds en fiducie à la date d'évaluation du 31 décembre 2013, même si le travail a débuté à l'automne 2013, le Comité conjoint a dû présenter aux Tribunaux une Requête pour proroger le délai prévu à l'article 10.01 (i) (ii) de la Convention;

16. Le 22 décembre 2014, le Comité conjoint a donc signifié et déposé à la Cour une *Requête du Comité conjoint pour faire prolonger le délai de la réévaluation des aspects financiers du Fonds au 31 décembre 2013* faisant état des différentes étapes accomplies et à finaliser pour les fins de la présente requête et demandait une prolongation du délai jusqu'au 16 mars 2015, le tout tel qu'il appert du dossier de la Cour;

17. En date des présentes, cette requête est toujours pendante devant la Cour et le Comité conjoint réitère sa demande de prolongation de délai pour autoriser la production de la présente requête;

LA PREUVE DOCUMENTAIRE :

18. Afin de permettre à la Cour de procéder à cette cinquième réévaluation triennale, le Comité conjoint soumet les documents suivants, dont copie a été remise et qui seront produites sous les cotes suivantes, à savoir :

R-1 Estimating the Prognosis of Canadians Infected with the Hepatitis C Virus through the Blood Supply 1986-1990, The Fifth Revision of Hepatitis C Prognostic Model based on the Post-Transfusion Hepatits C Compensation Claimant Cohort, Septembre 2014, préparé par Wendon Chen, Qilong Yi, William Wong et Murray Krahn, (le **"Rapport MMWG"**) joint à l'affidavit du Dr. Murray Krahn en date du 16 mars 2015;

R-2 Report of the Joint Committee Relating to the Financial Sufficiency of the 1986-1990 Hepatitis C Trust, as at December 31, 2010, en date du 16 mars 2015 (le "**Rapport du CC**");

R-3 Actuarial Report to the Joint Committee Assessing the Financial Sufficiency of the 1986-1990 Hepatitis C Trust as at December 31, 2013 en date du 11 mars 2015 préparé par Eckler Ltd (Richard Border et Wendy Harrison) (le "**Rapport Eckler**), joint à l'affidavit de Richard Border en date du 11 mars 2015;

R-4 Affidavit détaillé de Dr Vincent Bain et ses annexes, en date du 11 mars 2015;

L'INTERRELATION DES DIVERSES COMPOSANTES DE LA PREUVE DOCUMENTAIRE

19. Le Rapport MMWG et le Rapport Eckler sont tous deux fondés de façon significative sur les données relatives aux réclamations en vertu de la Convention compilées, dénominalisées et fournies par l'Administrateur. Ces données elles-mêmes ne sont pas produites auprès des Tribunaux mais ont été révisées par le Comité conjoint, le groupe de modélisation médicale MMWG et les actuaires retenus par le Comité conjoint (Eckler Ltd) et par le gouvernement fédéral (Morneau Sheppell). Les conclusions pertinentes tirées de ces données sont décrites dans le Rapport MMWG et le Rapport Eckler;

20. Le Rapport MMWG a été réalisé par un groupe formé d'épidémiologistes, de médecins, de statisticiens dirigé par le Dr. Murray Krahn de l'Université de Toronto. Lors de l'approbation de la Convention et de chacune des révisions triennales des aspects financiers du Fonds, le Dr. Krahn a formé un groupe de modélisation médicale pour développer et ensuite améliorer un modèle visant à estimer dans le temps l'évolution de l'état de santé des membres du recours (le modèle médical), le tout tel que décrit aux pages 6 et 7 du Rapport MMWG (R-1);

21. Le Comité conjoint soumet également l'affidavit du Dr. Vincent Bain, hépatologue, décrivant sommairement le virus de l'hépatite C, la progression de la maladie suite à l'infection, l'état de la science en matière de traitement ainsi que le pronostic de l'état de santé des patients infectés qui répondent bien aux traitements (élimination du virus), copie de cet affidavit étant joint au soutien des présentes sous la cote R-4;

22. Eckler Ltd a développé un modèle actuariel à partir du même logiciel utilisé pour élaborer le modèle médical. Le modèle actuariel incorpore notamment les éléments suivants :

a) le modèle médical;
b) les données concernant la performance des investissements effectués par le Fonds;
c) les critères à partir desquels les gouvernements provinciaux et territoriaux versent leurs contributions prévues à la Convention;
d) les données de la cohorte des réclamants pour évaluer le nombre de réclamations futures ainsi que leurs montants;
e) les informations concernant les différents médicaments, leurs coûts et leur efficacité;
f) les coûts annuels des services requis au terme de la Convention et fournis par les divers intervenants impliqués dans sa mise en oeuvre;

le tout tel qu'il appert plus amplement de l'Annexe J du Rapport Eckler (R-3);

23. Le Comité conjoint a également préparé un rapport résumant sa contribution au développement des hypothèses de travail utilisées par Eckler Ltd, faisant état des différents paiements effectués en vertu de la Convention, soulignant des problématiques rencontrées avec l'application de certains aspects de la Convention et décrivant le Programme VIH prévu à la Convention, copie de ce rapport est joint au soutien des présentes sous la cote R-2 (le Rapport du CC);

24. Même si, pour les fins de la révision triennale prévue à l'article 10.01 (1)(i), la Convention réfère au fonds en fiducie (soit les actifs en possession du fiduciaire), l'évaluation actuarielle implique l'ensemble de la fiducie telle que créée par la Convention, incluant, en plus des actifs investis, les « actifs théoriques » (*notional* assets) et les obligations financières, le tout tel qu'il appert plus amplement aux paragraphes 61 à 65 du Rapport Eckler (R-3);

25. Lors des deux dernières révisions triennales (au 31 décembre 2007 et au 31 décembre 2010), des différences ont été notées entre les évaluations actuarielles de Eckler Ltd et de Morneau Sheppell mais n'avaient pas été approfondies. Le montant cumulatif de ces différences lors de la révision triennale de 2010 était d'environ 200 millions, le tout tel que relaté à l'Annexe A du Rapport du CC (R-2);

26. Au début de la révision triennale 2013, le Comité conjoint et le Gouvernement Fédéral ont convenu d'un processus visant à éliminer les différences qui étaient basées sur des considérations techniques de modèles actuariels et qui ne relevaient pas d'une approche actuarielle, d'une philosophie ou d'hypothèses différentes. L'objectif visé étant de comprendre et d'expliquer les différences dans les résultats, les experts ont été encouragés à réduire autant que possible les différences de résultats découlant des techniques de modélisation différentes tout en ne compromettant pas leur indépendance. Ils ont ainsi échangé entre eux tout au long du processus ainsi qu'avec le groupe MMWG lors du développement du modèle médical, le tout tel qu'il appert notamment des paragraphes 257 à 260 et de l'annexe J du Rapport Eckler (R-3);

SOMMAIRE DE LA PREUVE DOCUMENTAIRE

27. Au 31 décembre 2013, 774 705 000$ avaient été versés aux membres du recours en vertu de la Convention. À la même date, les actifs du fonds s'élevaient à 1 190 199 000$. Déduction faite l'allocation d'actifs nécessaire pour protéger les membres du recours à l'encontre d'évènements défavorables majeures, les actifs de la fiducie excèdent les obligations d'un montant de 236 341 000$, le tout tel qu'il appert des paragraphes 20 et 247 du Rapport Eckler (R-3);

Les marges pour écarts défavorables (*margins for adverse deviations*)

28. L'analyse actuarielle établit d'abord les « meilleures estimations » (*best estimates*) basées sur des moyennes statistiques et qui ont 50% de probabilité d'être trop élevées et 50% de probabilité d'être trop basses. Les actuaires ajustent ensuite les obligations financières selon les marges pour écarts défavorables à même les obligations financières. Ces marges protègent contre une expérience un peu moins bonne que la moyenne prédirait. La marge pour écart défavorable est établie séparément pour chaque volet de compensation et calculée selon les risques connus qui y sont associés, le tout tel qu'il appert plus amplement des paragraphes 95 à 98 du Rapport Eckler (R-3);

29. La provision totale pour écarts défavorables ajoutées aux obligations financières est de 147 606 000$, tel qu'il appert des paragraphes 95 à 98 du Rapport Eckler (R-3);

30. La provision pour écarts défavorables est différente du coussin d'actifs (*buffer)* aussi appelé « capital nécessaire » (*required capital*) qui constitue une protection contre les évènements défavorables majeurs ou catastrophiques et mentionné plus loin. Bien que les deux représentent des protections contre un risque quantifiable, ils se distinguent sous deux aspects principaux. Premièrement, les marges pour écarts défavorables sont établies par rapport aux obligations et servent à augmenter les obligations financières alors que le capital nécessaire est une allocation théorique d'actifs additionnels en sus de ces obligations financières. Deuxièmement, les marges pour écarts défavorables protègent contre une expérience un peu moins bonne que l'hypothèse de meilleure estimation alors que le capital nécessaire fourni une protection contre les évènements défavorables majeurs ou catastrophiques. Finalement, la méthode utilisée pour calculer l'un et l'autre fait en sorte qu'il n'y a pas de double emploi, le tout tel que plus amplement décrit aux paragraphes 9 à 19, 95-96 et 216 à 219 du Rapport Eckler (R-3);

La taille de la cohorte des membres du recours

31. L'une des principales difficultés lors des révisions triennales antérieures était d'évaluer la taille de la cohorte des réclamants inconnus : ces personnes qui ne s'étaient pas manifester pour transmettre leur réclamation avant la date limite fixée au 30 juin pour faire une première réclamation;

32. Cette variable est maintenant mieux définie puisque la date limite est maintenant passée et que les protocoles proposés par le Comité conjoint concernant les exceptions déjà prévues à la Convention ont été approuvés par les Tribunaux et mis en application. L'incertitude est maintenant limitée au nombre de réclamations à venir qui sont visées par les protocoles approuvés par les Tribunaux et à savoir si un 3e protocole (proposé prématurément par le Comité conjoint selon le jugement de cette Cour) ou autre aménagement similaire sera un jour approuvé par les Tribunaux. Le Comité conjoint a demandé à Eckler Ltd de produire une analyse de sensibilité concernant cette éventualité, le tout tel qu'il appert des paragraphes 19 à 32 du Rapport du CC (R-2) et du paragraphe 253 du Rapport Eckler (R-3);

Les percées médicales en matière de traitement du VHC

33. Les percées des dernières années en matière de traitement font en sorte que la plupart des personnes infectées par le VHC peut être traitée de façon très efficace et avec moins d'effets secondaires qu'avec les traitements disponibles auparavant. Le taux de « réponse virale soutenue ou RVS» (*sustained viral response or SVR*) qui est l'expression utilisée pour parler de guérison suite au traitement du VHC, est de 95 à 99% pour certains génotypes (ou formes) du virus. Le plus faible taux de RVS est d'environ 80% avec les plus récents traitements, le tout tel que plus amplement décrit aux paragraphes 33 à 41 de l'affidavit du Dr. Bain (R-4);

34. Pratiquement toutes les personnes infectées par le VHC devrait être évaluées pour être traitées puisque les traitements actuels présentent moins de contre-indications et d'incompatibilités avec d'autres médicaments, moins d'effets secondaires (permettant aux personnes plus malades de supporter le traitement) et sont même efficaces chez des personnes qui ont été traitées antérieurement sans succès (sans RVS), le tout tel que plus amplement décrit aux paragraphes 41 à 52 de l'affidavit du Dr. Bain (R-4);

35. Malheureusement, une RVS ne garantit pas un retour à l'état de santé pré-infection, particulièrement parce que les membres du recours ont été infectés durant 10 à 30 ans et ont développé d'autres problèmes de santé. Toutefois, dans plusieurs cas, une RVS permet d'éviter de développer la maladie ou de faciliter le retour au travail ou la capacité de certaines personnes de vaquer à leurs tâches quotidiennes. Un suivi médical régulier n'est alors nécessaire que pour les personnes qui avaient développé une cirrhose avant de débuter le traitement, le tout tel qu'il appert des paragraphes 52 à 59 de l'affidavit du Dr. Bain (R-4);

36. Les coûts de ces nouveaux traitements se situent entre 50 000$ et 80 000$selon la durée du traitement et les médicaments prescrits. La Convention prévoit une indemnisation pour les traitements et médicaments non assurés par un régime public ou privé. À date, les nouveaux traitements sont couverts par quelques programmes d'assurance privée. Les gouvernements provinciaux étudient les nouveaux traitements lorsqu'ils sont approuvés mais la couverture d'assurance, si elle est offerte, tarde après l'approbation, tel que plus amplement décrit aux paragraphes 42 et 44 de l'affidavit du Dr. Bain (R-4);

37. Ces nouveaux traitements ont un effet significatif sur le modèle médical et les résultats actuariels. Le modèle actuariel prévoit un niveau élevé pour le montant de remboursement pour des frais médicaux durant les cinq prochaines années étant donné le coût des traitements et le nombre de personnes qui devraient être traitées. La compensation à long terme est réduite (par rapport aux évaluations antérieures) puisque plusieurs membres du recours devraient présenter une RVS améliorant leur état de santé ou évitant une détérioration de celle-ci, ces facteurs réduisant la probabilité ainsi que les montants de réclamations futures, le tout tel que décrit aux pages 9-10, 14 à 16, 27-28 et 49-50 du Rapport MMWG (R-1) ainsi qu'aux paragraphes 21 à 25, 134 à 148 et 208 à 211 du Rapport Eckler (R-3);

38. Eckler Ltd est d'avis que, par rapport à l'évaluation actuarielle au 31 décembre 2010, les changements apportés au modèle médical liés à l'arrivée des nouveaux traitements décrits ci-haut se traduiront par une réduction des obligations financières d'un montant de 370 000 000$. Cette réduction toutefois compensée par une augmentation des coûts de traitement de l'ordre de 146 000 000$. Étant donné l'incertitude de l'efficacité à long terme des nouveaux traitements, Eckler Ltd a ajouté une marge pour écarts défavorables allouant un taux d'efficacité à hauteur de 80% de celui prévu au modèle médical. Ceci entraîne une augmentation des obligations financières de 65 000 000$. Ainsi, l'impact net des nouveaux traitements sur les obligations financières est de 159 000 000$, le tout tel que plus amplement décrit aux paragraphes 21 à 25 ainsi qu'au tableau discuté au paragraphe 201 du Rapport Eckler (R-3);

Les restrictions à l'égard des réclamations pour perte de revenus

39. Au moment de l'approbation de la Convention par les Tribunaux, des restrictions ont été instituées à l'égard de certaines compensation étant donné que les obligations financières estimées étaient supérieures aux actifs prévus;

40. Au fil des années, ces restrictions ont été levées à l'exception de la limite de revenus bruts avant réclamation initialement fixée à 75 000$ qui a été haussée sans être complètement levée, tel que ci-haut relaté aux paragraphes 6, 7, 11 et 12 de la présente requête;

41. Depuis la dernière modification survenue en 2008, quatre réclamations impliquant un revenu brut pré-réclamation supérieur à 300 000$ ont été approuvées par le tribunal ayant juridiction avant d'être payées, le tout tel que discuté plus amplement aux paragraphes 40 et 41 du Rapport du CC (R-2);

Les conclusions concernant la suffisance financière

42. À la date d'évaluation du 31 décembre 2013, les actifs de la fiducie s'élèvent à 1 190 199 000$ incluant une somme de 1 028 048 000$ d'actifs investis et une somme de 162 152 000 d'actifs théoriques (les obligations financières restantes des gouvernements provinciaux et territoriaux prévues à la Convention et de l'Accord de financement). Les obligations financières, incluant une marge pour écarts défavorables, s'élèvent à la somme de 802 646 000$, le tout tel qu'il appert du paragraphe 20 du Rapport Eckler (R-3);

43. Le Comité conjoint a demandé à Eckler Ltd s'il était nécessaire ou approprié d'avoir un coussin entre la valeur estimée des actifs et celles des obligations financières en sus de la marge pour écarts défavorables ajoutée aux obligations financières. Eckler Ltd est d'avis, comme il l'était en 2010, que le fonds est assujetti à une volatilité importante découlant de diverses sources d'incertitude, tel qu'expliqué au paragraphe 214 du Rapport Eckler (R-3);

44. Eckler utilise une méthode actuarielle éprouvée pour bâtir un cadre spécifique pour le fonds pour calculer les risques quantifiables reliés au risque d'investissement et à l'inadéquation de taux d'intérêt, à l'incertitude liée au modèle médical (incluant l'efficacité des nouveaux traitements ainsi que la largeur des intervalles de confiance dans le développement statistique du modèle), les déviations individuelles des réclamants par rapport aux prédictions statistiques, l'expérience d'investissement, l'incertitude entourant les réclamations futures découlant de la variabilité dans les montants réclamés par les membres du recours, le tout tel que plus amplement discuté aux paragraphes 221 à 245 du Rapport Eckler (R-3);

45. L'objectif actuariel est d'identifier le montant de capitaux (actifs) nécessaire pour protéger les membres du recours contre une expérience défavorable majeure basé sur ces sphères de risque connues et quantifiables. La différence entre les actifs (investis et théoriques) et le montant d'actif nécessaire pour atteindre 95% de probabilité que le fonds pourra rencontrer ses obligations financières même si tous ces risques se matérialisaient en même temps est appelé le « capital nécessaire » (*required capital*). Le capital nécessaire est de 151 200 000$, représentant 18,8% des obligations financières, tel qu'il appert des paragraphes 216 à 220 et 246 du Rapport Eckler (R-3);

46. En tenant compte du capital nécessaire, l'excédent des actifs par rapports aux obligations financières calculé au 31 décembre 2013 est de 236 341 000$;

47. Eckler Ltd est d'avis que :

a) même si son modèle actuariel diffère de celui de Morneau Sheppell de par sa structure, les actuaires se sont entendus sur les hypothèses de travail importantes et ont utilisé le même modèle médical,
b) les différences de résultats des modèles actuariels sont modestes si l'on considère la taille du Fonds,
c) les deux modèles permettent de conclure que les actifs excèdent les obligations financières à la date d'évaluation du 31 décembre 2013, qu'il est approprié de prévoir une allocation d'actifs additionnels (*a buffer*) et qu'en tenant compte de cette allocation, les actifs excèdent les obligations financières,

le tout tel qu'il appert des paragraphes 216 à 220 et 246 du Rapport Eckler (R-3);

LES CONCLUSIONS RECHERCHÉES

48. À la lumière de la preuve documentaire, le Comité conjoint demande à la Cour de déclarer que le fonds en fiducie est financièrement suffisant à la date d'évaluation du 31 décembre 2013 conformément à l'article 10.01(1)(i) de la Convention de Règlement et qu'en tenant compte une allocation d'actifs nécessaire pour protéger les membres du recours de la survenance d'un événement défavorable majeur ou catastrophique, les actifs de la fiducie excèdent les obligations d'un montant de 236 341 000$;

49. Le Comité conjoint invite également la Cour à rendre les directives appropriées concernant la tenue d'une audition ultérieure afin de statuer sur les questions financières sous-jacentes suivantes conformément à la Convention approuvée par les tribunaux :

a) Est-ce que la restriction qui subsiste sur les paiements en vertu des Régimes, concernant l'approbation préalable par le tribunal ayant juridiction, devrait être modifiée ou abolie, selon l'article 10.01(1)(i)A de la Convention de Règlement?

b) Est-ce qu'une portion des fonds et des autres éléments d'actifs détenus par le fiduciaire en vertu de la Convention de Règlement peut être déclarée comme ne faisant pas l'objet d'une attribution actuarielle, selon le texte des jugements d'approbation (Cour Supérieure du Québec, le 19 novembre 1999, Annexe F, par. 1)?

c) Dans l'affirmative, est-ce que, dans le cadre du libre exercice de leur pouvoir discrétionnaire prévu aux Jugements d'approbation, la Cour ordonne que ces fonds et autres éléments d'actifs fassent l'objet d'une attribution selon le paragraphe 1 de l'Annexe F?

d) Dans l'affirmative, préciser de quelle façon devra être effectuée cette attribution.

50. Une requête au même effet sera également présentée devant l'Honorable Juge en Chef Winkler en Ontario et devant l'Honorable Juge en Chef Bauman en Colombie-Britannique;

51. La présente requête est bien fondée en faits et en droit;

PAR CES MOTIFS, PLAISE À LA COUR :

ACCUEILLIR la présente requête;

PROROGER le délai prévu à l'article 10.01(1)(i) jusqu'au 16 mars 2015;

DÉCLARER que le fonds en fiducie est suffisant du point de vue financier à la date d'évaluation du 31 décembre 2013;

DÉCLARER qu'en tenant compte d'une allocation d'actifs nécessaires pour protéger les membres du recours à l'encontre d'un événement défavorable majeur ou catastrophique, les actifs de la fiducie excèdent les obligations d'un montant de $236 341 000;

RENDRE toute directive ou ordonnance qu'elle jugera appropriée selon les termes de la Convention;

DÉCLARER que le jugement à intervenir sur la présente requête ne prendra effet qu'à compter du moment où des ordonnances similaires auront été rendues par les tribunaux de l'Ontario et de la Colombie-Britannique;

LE TOUT sans frais.

MONTRÉAL, le 16 mars 2015

(s) Savonitto & Ass. Inc.

SAVONITTO & ASS. INC.
Procureurs du Requérant Me Michel Savonitto, es-qualité de membre du Comité conjoint

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Procureurs

AFFIDAVIT

Je, soussignée, **MARTINE TRUDEAU**, avocate, exerçant ma profession au sein de l'étude Savonitto & Ass. inc., sise au 450 rue St-Pierre, suite 101, en les cité et district de Montréal, affirme solennellement ce qui suit :

1. J'assiste le Membre du Comité conjoint pour le Québec, dans le cadre du présent dossier et agissant comme requérant pour les fins de la présent;

2. Tous les faits allégués à la présente requête sont vrais au meilleur de ma connaissance;

ET J'AI SIGNÉ :

(s) Martine Trudeau

MARTINE TRUDEAU

Affirmé solennellement devant moi
à Montréal, ce 16 mars 2015

Line Gagnon # 141 094

Commissaire à l'assermentation

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Procureurs

AVIS DE PRÉSENTATION

Me Nathalie Drouin
Me Pascale-Catherine Guay
Procureurs de l'intimé
PROCUREUR GÉNÉRAL DU CANADA/
ATTORNEY GENERAL OF CANADA
Complexe Guy Favreau Tour Est
200, boul. René Lévesque Ouest, 5e étage
Montréal (Québec) H2Z 1X4

Me Manon Des Ormeaux
BERNARD, ROY (JUSTICE-QUÉBEC)
Ministère de la Justice du Québec
Service du contentieux
1, rue Notre-Dame Est
Bureau 8.00
Montréal (Québec) H2Y 1B6

Me Mason Poplaw/Me Philippe Dufort-Langlois
McCARTHY TÉTRAULT
1000, rue de la Gauchetière Ouest
Bureau 2500
Montréal (Québec) H3B 0A3

PRENEZ AVIS que la présente **REQUÊTE POUR DIRECTIVES PRÉSENTÉE PAR LE MEMBRE DU COMITÉ CONJOINT AUX FINS DE RÉÉVALUER LES ASPECTS FINANCIERS DU FONDS** (Art. 10.01 (1) (i) (ii) de la Convention) sera présentée à Toronto devant l'Honorable François Rolland, Juge en chef de la Cour supérieure du Québec, les 22 et 23 juin 2015 selon les modalités qu'il lui plaira de fixer.

VEUILLEZ AGIR EN CONSÉQUENCE.

MONTRÉAL, le 16 mars 2015

(s) Savonitto & Ass. Inc.

SAVONITTO & ASS. INC.
Procureurs du Requérant Me Michel Savonitto, es-qualité de membre du Comité conjoint

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C A N A D A
PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000016-960

C O U R S U P É R I E U R E
Recours Collectifs

DOMINIQUE HONHON

Requérante

-c-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Intimés

-et-

ME MICHEL SAVONITTO, es-qualité de membre du Comité conjoint

REQUÉRANT

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A
PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000068-987

C O U R S U P É R I E U R E
Recours Collectifs

DAVID PAGE

Requérant

-c-

PROCUREUR GÉNÉRAL DU CANADA

PROCUREUR GÉNÉRAL DU QUÉBEC

SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Intimés

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

INVENTAIRE DES PIÈCES REMISES
(Requête pour directives présentée par le membre du Comité conjoint aux fins de réévaluer les aspects financiers du Fonds)

PIÈCE R-1 : Estimating the Prognosis of Canadians Infected with the Hepatitis C Virus through the Blood Supply 1986-1990, The Fifth Revision of Hepatitis C Prognostic Model based on the Post-Transfusion Hepatits C Compensation Claimant Cohort, Septembre 2014, préparé par Wendon Chen, Qilong Yi, William Wong et Murray Krahn, (le **"Rapport MMWG"**) joint à l'affidavit du Dr. Murray Krahn en date du 16 mars 2015;

PIÈCE R-2 : Report of the Joint Committee Relating to the Financial Sufficiency of the 1986-1990 Hepatitis C Trust, as at December 31, 2010, en date du 16 mars 2015 (le "**Rapport du CC**");

PIÈCE R-3 : Actuarial Report to the Joint Committee Assessing the Financial Sufficiency of the 1986-1990 Hepatitis C Trust as at December 31, 2013 en date du 11 mars 2015 préparé par Eckler Ltd (Richard Border et Wendy Harrison) (le "**Rapport Eckler**), joint à l'affidavit de Richard Border en date du 11 mars 2015;

PIÈCE R-4 : Affidavit détaillé de Dr Vincent Bain et ses annexes, en date du 11 mars 2015;

PIÈCE R-5 : Jugement rendu par l'Honorable Nicole Morneau le 19 novembre 1999 et annexe F;

MONTRÉAL, le 16 mars 2015

(s) Savonitto & Ass. Inc.

SAVONITTO & ASS. INC.
Procureurs du Requérant Me Michel Savonitto, es-qualité de membre du Comité conjoint

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C A N A D A
PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

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DOMINIQUE HONHON

Requérante

-c-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Intimés

-et-

ME MICHEL SAVONITTO, es-qualité de membre du Comité conjoint

REQUÉRANT

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

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Intimés

-et-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-et-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

AFFIDAVIT OF MURRAY KRAHN
(sworn March 16, 2015)

I, Murray Krahn, MD MSc FRCPC, of the Department of Medicine and Faculty of Pharmacy, University of Toronto, located at The Toronto General Hospital, EN14-207, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4, Canada, MAKE OATH AND SAY:

1. I am Director of the Toronto Health Economics and Technology Assessment Collaborative of the Department of Medicine and Faculty of Pharmacy of the University of Toronto.

2. I am also the senior member of what is known as the medical model working group ("**MMWG**"). While the composition of the MMWG has changed over time, I have been involved since its inception in 2002. The MMWG has provided medical modeling expert advice and reports to the Joint Committee of the 1986-1990 Hepatitis Settlement Agreement for the purposes of the triennial fund sufficiency reviews under that settlement agreement. For the most recent financial sufficiency review triggered at December 31, 2013, the MMWG prepared a report entitled "Estimating the Prognosis of Canadians Infected with the Hepatitis C Virus Through The Blood Supply, 1986-1990 - The Fifth Revision of Hepatitis C Prognostic Model Based on the Post-Transfusion Hepatitis C Compensation Claimant Cohort". A copy of that report is attached as Exhibit "A".

3. The other members of the MMWG who participated in the preparation of this report are Dr. Wendong Chen of the Toronto Health Economics and Technology Assessment Collaborative of the Department of Medicine and Faculty of Pharmacy of the University of Toronto, Dr. Qilong Yi of Canadian Blood Services and the University of Ottawa Faculty of Medicine, Epidemiology and Community Medicine and Dr. William Wong of the Toronto Health Economics and Technology Assessment Collaborative of the Department of Medicine and Faculty of Pharmacy of the University of Toronto. Dr. Wendong Chen did significant portions of the data review, medical literature review and rewriting of the report for this revision. Dr. Yi did significant portions of the data analysis and review. I oversaw the MMWG and reviewed the report before it was issued.

4. I certify that the members of the MMWG are aware that our duties are:

(a) to provide opinion evidence that is fair, objective and non-partisan and related only to matters within our area of expertise; and

(b) to assist the courts and provide such additional assistance as the courts may reasonably require to determine a matter in issue.

5. Members of the MMWG are aware that the foregoing duties prevail over any obligation we may owe to any party on whose behalf we are engaged and we are aware that we are not to be advocates for any party. I confirm that the report conforms with the above-noted duties. I further confirm that if called upon to give oral or written testimony, I or the other members of the MMWG will give such testimony in conformity with these duties.

6. My curriculum vitae is attached as Exhibit "B". The curricula vitae of Drs. Chen, Yi and Wong are attached, respectively, as Exhibits "C", "D" and "E".

MURRAY KRAHN

SWORN BEFORE ME at the City of Toronto, in the Province of Ontario, on March 16, 2015.

Commissioner for Taking Affidavits

This is Exhibit "A" referred to in the Affidavit of Murray Krahn sworn before me, this 16th day of March, 2015

A COMMISSIONER FOR TAKING AFFIDAVITS

Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus through the Blood Supply, 1986-1990

The Fifth Revision of Hepatitis C Prognostic Model Based on the Post-Transfusion Hepatitis C Compensation Claimant Cohort

September 2014

Wendong Chen MD PhD
Qilong Yi MD MSc PhD
William Wong PhD
Murray Krahn MD MSc FRCPC

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List of Abbreviations

AE, adverse event

CASL, Canadian Association for the Study of the Liver

CHC, chronic hepatitis C

CI, confidence interval

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

HIV, human immunodeficiency virus

MMLE, Markov maximum likelihood estimation

PEG-IFN, pegylated interferon

RBV, ribavirin

RNA, ribonucleic acid

RR, risk ratio/relative risk

SD, standard deviation

SE, standard error

SVC, spontaneous viral clearance

SVR, sustained viral response

US FDA, United States Food and Drug Administration

MMWG, medical model working group

Executive Summary

The hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Prior to the availability of serologic testing for the presence of hepatitis C in 1990, blood transfusion and the use of blood products were the main sources of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to prevent the transmission of viral hepatitis in the general population. However, this practice was not conducted in Canada and as a result many Canadians likely acquired HCV through blood transfusion or blood products during this timeframe. On March 27, 1998 Canadian federal, provincial, and territorial governments announced an offer of financial assistance to individuals who acquired HCV through the blood system between January 1, 1986 and July 1, 1990. In 1999, court orders in British Columbia, Ontario and Québec were obtained approving a settlement agreement which established a compensation fund of approximately $1.1 billion for those Canadians who acquired HCV through blood transfusion or blood products between January 1, 1986 and July 1, 1990.

In order to assist with planning for future compensation, a working group was formed in November of 1998 to provide the best possible estimates for the prognosis of transfusion-acquired HCV claimants who met compensation requirements. A Markov state-transition model, developed to simulate the long-term liver-related health outcomes of compensation claimants, provided data needed for an actuarial model used in future compensation fund estimations. The compensation agreement between governments and plaintiffs requires fund estimates to be reviewed every three years as the accuracy of previous predictions may be substantially affected by newly approved compensation claimants, new antiviral treatments, and updates in the natural

history of HCV. The original HCV prognostic model which simulated approved compensation claimants has undergone a total of five subsequent revisions including the current iteration documented in this current report. The first revision was conducted in 2002 by a working group consisting of five members (Murray Krahn, Jenny Heathcote, Linda Scully, Peter Wang, and Qilong Yi). That revision explicitly linked compensation levels with the stage of liver fibrosis in 2,466 approved compensation claimants. The second revision was conducted in 2005 and one new member (Morris Sherman) was added to the working group. The second revision utilized Markov maximum likelihood estimation (MMLE) to determine stage-specific transition probabilities that were applied to the HCV prognostic model to predict liver-related complications and mortality in 4,530 approved claimants. Also included in the second revision of the HCV prognostic model was a survey of treatment patterns in Canadian hepatologists. That survey incorporated treatment data related to use of the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy which has since replaced conventional interferon-based therapies. The third revision was conducted in 2007 by a working group consisting of three members (Murray Krahn, Qilong Yi, and Hla-Hla Thein). That revision primarily updated baseline information of 5,004 approved compensation claimants and included a more comprehensive meta-analysis to estimate stage-specific transition probabilities. The fourth revision was conducted in 2010 by the same working group as the third revision. That revision maintained the same objectives as before and modified the model structure to include information regarding the transition from hepatocellular carcinoma (HCC) to liver transplantation as well as adopting treatment patterns derived from the claimant cohort.

Since the fourth revision, several new and highly effective antiviral regimens have been developed, some of which are currently available in Canada. Because the new antiviral regimens provide a cure rate of between 70% and 90%, treatment patterns are expected to change substantially and will likely have a significant impact on the prognosis of compensation claimants. Thus, the fifth revision of the HCV prognostic model was requested and a working group consisting of four members (Wendong Chen, Qilong Yi, William Wong, and Murray Krahn) was established in the fall of 2013 to undertake the current revision. The current revision incorporates the result of an on-line survey study of physicians treating HCV patients in Ontario to estimate future treatment patterns with new antiviral regimens, maximizes the use of claimant cohort data to estimate model variables, and revises model predictions for the surviving compensation claimants as of August 31, 2013.

According to the collected claims data as of August 31, 2013, 3,832 surviving compensation claimants, including 884 hemophilics and 2,948 non-hemophilics, were identified to create the claimant cohort for model simulations. The treatment pattern survey attempted to elicit choices for existing standard antiviral therapy, PEG-IFN/RBV, as well as three new types of antiviral regimens (PEG-IFN/RBV-based triple therapy with boceprevir, telaprevir, or faldaprevir; sofosbuvir-based doublets with daclatasvir, ledipasvir or simeprevir; and three direct-acting antiviral regimens plus RBV) in claimants stratified by their status of previous treatment and human immunodeficiency virus (HIV) co-infection. Systematic reviews of randomized clinical trials assessing the three new antiviral regimens were conducted to estimate their treatment efficacy and safety that are needed when developing treatment pattern survey and revising HCV prognostic model. The 1986-1990 HCV Claim Center also conducted a survey of previously

treated claimants to estimate sustained viral response (SVR), the indicator for viral clearance, after previous treatments in current surviving claimants. In order to further improve internal validity of model variables, the current revision has used claims data as the primary data source to estimate the initial distribution of fibrosis stages, natural history of HCV, and non-liver-related mortality for the revised HCV prognostic model. The revised HCV prognostic model has been validated by comparing predicted and observed cumulative rates of liver-related complications and mortality from 2003 to 2013 in treatment-naïve non-hemophilic claimants (decompensated cirrhosis: 6.1% vs. 7.4%; HCC: 1.9% vs. 1.8%; liver transplantation: 0.7% vs. 0.7%; liver-related mortality: 4.1% vs. 7.4%).

By running 50,000 iterations in the revised HCV prognostic model to simulate surviving claimants as of August 31, 2013, the cumulative rates of decompensated cirrhosis, HCC, liver transplantation, and liver-related mortality in the surviving claimants by 2070 are predicted to be 12.1%, 4.3%, 0.9%, and 14.7%, respectively. Further comparisons of model outputs for claimants stratified by their hemophilic status predict that hemophilic claimants will have doubled cumulative rates of liver-related complications (decompensated cirrhosis: 20.7% vs. 9.5%; HCC: 7.3% vs. 3.4%) and mortality (24.9% vs. 11.6%) by 2070 when compared with non-hemophilic claimants. Because the new antiviral regimens are likely to cure most claimants, the long-term prognosis of claimants would be mainly determined by the initial proportions of cirrhosis and liver-related complications. The model outputs of claimants stratified by age strata predict that hemophilic claimants under the age of 80 years will have doubled lifetime cumulative rates of liver-related complications and mortality mainly due to higher initial proportions of cirrhosis.

The current revision has performed sensitivity analyses to assess the impact of major revisions on model predictions. The updated treatment patterns in the current revision are found to reduce cumulative rates of liver-related complications and mortality by half in non-hemophilic claimants when compared to the treatment patterns applied in the fourth revision that was conducted in 2010. Except that the updated lifetime risk of liver transplantation is substantially reduced (0.9% vs. 3.2%), the updated model predictions are not sensitive to changing data source used to estimate model variables for the prognosis of cirrhosis and non-liver-related mortality. Finally, the impact on overall uncertainty associated with model variables on model outputs are explored using two-order Monte Carlo simulation approach and presented with the 95% confidence intervals of their cumulative rates of liver-related complications in 2070 (decompensated cirrhosis: 8.7% to 15.5%; HCC: 3.1% to 5.5%) and mortality (11.0% to 18.4%).

1. Background

HCV is identified as one of the most common causes of liver disease in Canada. Recent studies suggest that the prevalence of HCV infection in the Canadian population is about 0.8 % with an estimated 250,000 to 300,000 Canadians living with HCV.[1-3] Blood transfusion and blood products were the main sources of HCV infection prior to 1990 when serological testing methods came into use for HCV screening in blood donors.[4] Surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of non-A non-B viral hepatitis in the general population from 1986 to 1990 before HCV was discovered.[5] However, surrogate marker testing was not employed in most Canadian jurisdictions[6] and as a result many individuals in Canada likely acquired HCV via blood transfusion or blood products during this four-year period.

On March 27, 1998, federal, provincial, and territorial governments announced an offer of financial assistance to individuals who acquired HCV either directly or indirectly through the blood system between January 1, 1986 and July 1, 1990. Up to $1.1 billion was to be made available to compensate individuals which included hemophilics, secondarily infected HCV claimants, those with HIV who became co-infected with HCV, as well as any others with an HCV infection acquired through blood transfusion during the period in question. In order to settle on an appropriate compensation scheme, the federal and provincial governments as well as the claimants reviewed a number of models of the natural history of HCV. Because of disagreement regarding the natural history of this disease, the Canadian Association for the Study of the Liver (CASL), an impartial body with no stake in the outcome of compensation negotiations, was approached by both stakeholders to produce the best available model simulating the natural history of HCV. In November of 1998, CASL met with individuals with

expertise in hepatitis C epidemiology, hepatitis C clinical care, and decision modeling to assist in the construction of a prognostic model for HCV. These meetings led to the formation of an ad-hoc working group comprised of Drs. Murray Krahn, Jenny Heathcote, Linda Scully, Leonard Seeff and John Wong. This working group evaluated and accepted the structural validity of a simplified version of the Bennet/Wong Markov chain model.[7,8] The working group reviewed each parameter in the model and updated several key parameters, including the excess mortality rate and the incidence rates of cirrhosis, HCC and decompensated cirrhosis, by systematic review of relevant literature. Confidence intervals (CI) and/or plausible ranges were also estimated for key model parameters. With this revised model, the cumulative probability of acquiring cirrhosis, decompensated liver disease, and liver-related death were predicted using baseline characteristics of compensation claimants. For the transfusion cohort as a whole, the 20-year and lifetime cumulative probability of developing liver cirrhosis was 13.4% and 24.9%, respectively. Similarly, the 20-year and cumulative lifetime probability of dying from HCV-related liver disease was 2.5% and 12.3%, respectively. However, the rapid development of HCV treatment options coupled with accumulated clinical information on the natural history of HCV within the compensation cohort have led to a clear demonstration for the need to regularly revise model predictions of long-term prognosis in approved compensation claimants. Doing so will ensure the sufficiency of compensation funds in the future. As well, the compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the fund every three years. Four revisions have been conducted thus far (in 2002, 2005, 2007, and 2010) by taking into account the updates on treatment patterns and the natural history of HCV in the approved compensation claimants.

The first revision was conducted in 2002 by a working group consisting of three members from the original research team (Drs. Jenny Heathcote, Linda Scully and Murray Krahn) along with two new members, Dr. Peter Wang (Epidemiology) and Dr. Qilong Yi (Biostatistics). This revision modified the original prognostic model as a fibrosis stage-based Markov model and updated transition probabilities between fibrosis stages using literature-based evidence. This updated Markov model was used to predict the long-term prognosis of compensation claimants over their remaining lifetimes in accordance with HCV severity levels as stipulated in the compensation package.

The second revision of the HCV prognostic model was conducted in 2005. This revision included an updated literature review which was used to estimate transition probabilities and integrated the most updated claims data at that time for model predictions. The third revision was conducted in 2007 and retained the objectives of the second revision along with a fine-tuning of methodology in order to obtain more accurate predictions. The working group conducting the third revision included two members from previous revisions (Drs. Murray Krahn and Qilong Yi) and one new member, Dr. Hla-Hla Thein, who joined the team as a consultant and modeling expert. The fourth revision was conducted by the same working members as in the 2007 revision. This revision categorized claimants into different disease stages based on clinical symptoms and results from laboratory tests. As well, the fourth revision added the transition from HCC to liver transplantation and incorporated treatment pattern data derived from the claimant cohort. The antiviral therapy employed in the fourth revision was the combination of PEG-IFN and RBV. This treatment combination was recommended by clinical practice guidelines at the time of revision.[9]

A number of significant advances have been made for treating CHC since the fourth revision. Boceprevir and telaprevir, two molecules which inhibit HCV replication through binding to active sites of HCV non-structural protein,[10,11] were approved by Health Canada in 2011. These two agents increased SVR rate at 24 weeks, the indicator of a clinical cure for HCV,[12] to over 50% when combined with PEG-IFN/RBV in both treatment-naïve[13,14] or previously treated patients[15,16] with viral genotype 1, the most prevalent genotype (about 70%) in Canadian patients with CHC.[17] In December 2013, Health Canada approved two additional antiviral agents, simeprevir (NS3/4A protease inhibitor) [18] and sofosbuvir (the nucleotide analog NS5B polymerase inhibitor).[19] The combination of these two antiviral agents may provide a cure for more than 90% of treatment-naïve or previously treated viral genotype 1 patients. In addition, this regimen has a much better safety profile and only needs 12 weeks treatment time,[20] while PEG-IFN/RBV usually requires 48 weeks for treatment and causes a series of side effects decreasing treatment compliance. Several other protease inhibitors have been also evaluated by phase II or III trials and they are expected to be launched in Canada within the next year or two. For example, current phase II studies have demonstrated that faldaprevir, a potent, once-daily, HCV NS3/4A protein inhibitor, could produce a doubling of antiviral response when combined with PEG-IFN/RBV in treatment-naïve patients.[21] Sofosbuvir-based doublets with ledipasvir (an inhibitor of the hepatitis C virus HCV NS5A protein) [22,23] or daclatasvir (HCV NS5A replication complex inhibitor) [24] could provide a cure for nearly all treatment-naïve or previously treated viral genotype 1 patients within 12 weeks. The combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r), the NS5A inhibitor ombitasvir, and the nucleoside polymerase

inhibitor dasabuvir, which are direct-acting antiviral agents known as "3D", could cure 96% of treatment-naïve or previously treated viral genotype 1 patients when combined with RBV.[25]

The emergence of highly effective and safe antiviral regimens is expected to have a profound impact on treatment patterns in patients with CHC, potentially resulting in an end to the era of interferon-based treatment for CHC.[26] Even though the abovementioned new antiviral regimens are extremely costly, the reimbursement policy for this compensation claimant cohort could accelerate the uptake of these regimens, dramatically improving the long-term prognosis of current surviving claimants chronically infected with HCV. Thus, a fifth revision of the HCV prognostic model has been requested to estimate future treatment patterns affected by newly launched and upcoming antiviral regimens and revise model outputs of current surviving claimants accordingly. Additionally, previous revisions of the HCV prognostic model were mainly based on literature-derived model variables because the claimant cohort had a relatively small sample size and limited follow-up time. In order to further improve internal validity of model predictions, the current revision has taken the claims data as its data source to estimate model variables for fibrosis progression, prognosis of cirrhosis, and non-liver-related mortality for the purpose of further improving accuracy of model predictions. A working group consisting of two members (Drs. Murray Krahn and Qilong Yi) from previous working groups along with two new members (Drs. Wendong Chen and William Wong) was created to undertake the fifth revision of the HCV prognostic model and model outputs of current surviving compensation claimants as of August 31, 2013. Dr. Wendong Chen has developed the revision plan, led the revision, and prepared this report.

2. Revisions on HCV prognostic model

2.1. Revisions on model structure

The HCV prognostic model used in the fourth revision has been modified to meet the objectives of the current revision. The HCV prognostic model in the current revision remains as a fibrosis stage-based Markov model. The health states in this model include fibrosis stages classified as 0 to 4 (F_0 to F_4), liver-related complications (decompensated cirrhosis, HCC, liver transplantation, and post-transplant), and death that is further classified as liver-related death and non-liver-related death. Liver-related death is defined as death with prior occurrence of any liver-related complications. The current revision also allows fibrosis to progress in one direction ($F_0 \rightarrow F_1 \rightarrow F_2 \rightarrow F_3 \rightarrow F_4$). However, the fibrosis stages prior to compensated cirrhosis are assumed to stop progression once viral clearance is achieved through spontaneous viral clearance (SVC) or SVR after antiviral therapy. Because compensated cirrhosis still progresses to decompensated cirrhosis or HCC at a lower rate even after successful antiviral therapy,[27] the current revision adds the transitions from compensated cirrhosis with viral clearance to decompensated cirrhosis and HCC in the HCV prognostic model. The current revision also keeps the assumptions made in the fourth revision regarding the rare incidences of HCC and SVC associated with fibrosis stages prior to F_4 in the model. A simplified representation of the structure of the revised HCV prognostic model in the current revision is illustrated in *Figure 1*. Potential transitions associated with each health state in the model are also depicted in *Figures 2 to 10*. The current revision used TREEAGE PRO 2013 to construct the HCV prognostic model and run microsimulation analyses to generate model outputs predicting long-term prognosis of surviving compensated claimants.

2.2. Revisions on model variables

The model variables in the HCV prognostic model include initial distribution of health states, updated treatment patterns, treatment efficacy of antiviral regimens, fibrosis progression, prognosis of cirrhosis, and non-liver-related mortality. Because hemophilic claimants are substantially different from non-hemophilic claimants in age, gender, and comorbidities that can strongly affect disease prognosis, the current revision estimates model variables according to the hemophilic status of claimants in order to generate model outputs for hemophilic and non-hemophilic claimants separately.

2.2.1. Initial distribution of health states

The 1986-1990 Hepatitis C Claims Center provided claims data for 5,368 approved claimants as of August 31, 2013. When compared to the approved claimants (n=5,225) in the last revision performed in 2010, the current claimant cohort includes 143 newly approved claimants. The proportion of hemophilia in the approved 5,368 claimants is 25.1%. The hemophilic claimants differ from non-hemophilic claimants regarding the distributions of male gender (88.4% vs. 52.6%, $p<0.001$) and HIV co-infection (30.6% vs. 3.1%, $p<0.001$). Similar differences in male gender and HIV co-infection between hemophilics and non-hemophilics are also observed in the 3,832 surviving compensation claimants (884 hemophilics and 2,948 non-hemophilics). Additionally, surviving hemophilics are about 12 years younger than surviving non-hemophilics (mean age: 49.7 years vs. 61.8 years, $p<0.001$). Unadjusted comparisons of baseline demographic and clinical characteristics between hemophilic and non-hemophilic claimants are summarized in *Table 1*.

According to the collected treatment records of compensation claimants, about a quarter of compensation claimants (n=1,342) were treated previously. Because the previously treated claimants are not followed up for their treatment outcomes, the claims center has conducted a telephone survey to trace the treatment outcomes in those previously treated claimants. Based on the surveyed claimants giving the information on the outcomes of previous antiviral treatments, 273 out of 454 (60%) surveyed claimants achieved SVR after previous antiviral treatments. Non-hemophilic claimants experienced a better treatment response than hemophilic claimants (SVR rate: 61.6% vs. 46.6%, p=0.001) even though the viral genotype distributions in the two groups were highly comparable. The surveyed claimants have similar baseline characteristics as the entire cohort of surviving claimants. For example, the surveyed hemophilic claimants are also associated with much higher proportions of male, HIV co-infection, and advanced disease stages than the surveyed non-hemophilic claimants (*Table 2.1*). These differences explain the poorer treatment response associated with the surveyed hemophilic claimants.[28,29,30] The comparisons of the baseline characteristics between surveyed hemophilic and non-hemophilic claimants in treatment responders and non-responders (*Table 2.2 and 2.3*) further suggest that the younger age and higher proportions of male and HIV co-infection associated with surveyed hemophilics are not affected by treatment response. However, the proportion of advanced compensation level is significantly higher in the surveyed hemophilic claimants with SVR (7.3% vs. 1.4%, p=0.032). Given that treatment outcomes are not tracked in the claim cohort data, the patterns of baseline characteristics found in the surveyed claimants stratified by SVR status and hemophilic status are used to estimate initial distribution of compensation levels in previously treated claimants. The initial distribution of compensation levels in the treatment-naïve claimants stratified by the status of hemophilia and HIV co-infection is then estimated directly from claims data (*Table 3*).

Because the HCV prognostic model is a fibrosis stage-based state transition (i.e. Markov) model, the initial distribution of compensation levels derived from the current claimant cohort are further converted to the initial distribution of fibrosis stages using the established matching relationship between compensation levels and fibrosis stages in previous revisions. The matching principles are stated below.

- Compensation level 1: F_0 with negative HCV RNA;
- Compensation Level 2: F_0 with positive HCV RNA;
- Compensation level 3: F_1 or F_2 indicating non-bridging fibrosis;
- Compensation level 4: F_3 indicating bridging fibrosis;
- Compensation level 5: F_4 with compensated cirrhosis;
- Compensation level 6: F_4 with decompensated cirrhosis, HCC, and/or post-transplant.

Because only 19.6% of approved claimants had a documented liver biopsy to confirm their compensation level, assessing liver disease severity using compensation level alone could introduce significant uncertainty regarding the true initial distribution of fibrosis stages in the current surviving claimants. Thus, the current revision continues to use the propensity score matching method[31,32] developed in the fourth revision to estimate fibrosis stage distribution in the claimants without liver biopsy. This method includes the following steps.

Step 1. A multiple logistic regression analysis is performed using biopsy status as the dependent variable and age, gender, previous treatment, hemophilic status, and HIV status as independent variables. Claimants with decompensated cirrhosis or HCC are excluded for propensity score matching as the diagnoses of these two complications are

usually based on symptoms and imaging. Claimants with compensation level 1 are also excluded because individuals with a negative HCV RNA status typically do not have hepatic fibrosis. Thus, this multiple logistic regression analysis only includes claimants with compensation levels of 2 through 5.

Step 2. The formula derived in *Step 1* is used to calculate a propensity score. This score is defined as the predicted probability of receiving a liver biopsy for each included claimant. The derived formula is as follows:

Log [p/(1-p)] = a + age*b1 + gender*b2 + previous treatment*b3 + hemophiliacs status*b4 + HIV status*b5;

p is the probability of receiving liver biopsy;

a is the intercept parameter in the multiple logistic regression analysis;

b1....b5 are the coefficients associated with independent variables in the multiple logistic regression analysis.

Step 3. Claimants are stratified on the basis of propensity scores of <0.4 and > 0.4. In each group, we assume that claimants without liver biopsy have the same distribution of fibrosis stage as the claimants who received a liver biopsy if they have the same compensation level.

The current revision has used this method to estimate the initial distribution of fibrosis stages in the surviving hemophilic claimants and non-hemophilic claimants, respectively. The adjusted initial proportions of F_0 with negative HCV RNA, F_0 with positive HCV RNA, F_1/F_2, F_3, compensated cirrhosis, decompensated cirrhosis, HCC, and post-transplant in current surviving hemophilic claimants are 15.8%, 20.3%, 17.8%, 23.3%, 18.1%, 2.9%, 1.3%, and 0.6%,

respectively (*Table 4.1*). The adjusted initial proportions of F_0 with negative HCV RNA, F_0 with positive HCV RNA, F_1/F_2, F_3, compensated cirrhosis, decompensated cirrhosis, HCC, and post-transplant were 17.5%, 33.3%, 26.9%, 10.7%, 8.6%, 1.7%, 0.5%, and 0.7%, respectively (*Table 4.2*).

2.2.2 Efficacies of new antiviral regimens

The medical model working group (MMWG) on the current revision has searched the websites of Health Canada and the United States Food and Drug Administration (US FDA) for newly approved antiviral agents since 2010. As of January 31, 2014, the approved new antiviral agents in both Canada and the United States include boceprevir,[33,34] telaprevir,[35,36] sofosbuvir,[37,38] and simeprevir.[39,40] The MMWG on the current revision has also reviewed the results of recently completed phase III trials evaluating new antiviral regimens for CHC and consulted the hepatologists at the University Health Network (Drs. Jordan Feld, David Wong, and Morris Sherman) for their opinions on any new antiviral agents that could be available to Canadian patients in the next two years. Based on the identified clinical evidence, expert opinions, and discussions among the members of working group, the updated treatment patterns in the current revision have taken into account four antiviral regimens, including current standard treatment with PEG-IFN/RBV; PEG-IFN/RBV-based triple therapy with boceprevir, telaprevir, or faldaprevir; sofosbuvir-based doublets with simeprevir, daclatasvir, or ledipasvir; and 3D regimen plus RBV, in the updated treatment patterns over the next five years in compensation claimants. Thus, the current revision has conducted a systematic review to estimate treatment efficacy and safety of the four selected antiviral regimens that are included in the treatment preference survey study and the revised HCV prognostic model.

The current revision has searched the common medical databases (MEDLINE, EMBASE, Web of Science, and The Cochrane Library) and proceedings of the annual conferences of the American Association of Study Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), the two major international organizations for viral hepatitis, for any published randomized trials assessing the selected new antiviral regimens since 2010. Single-arm meta-analysis method is used to estimate overall SVR and adverse event (AE)-related treatment discontinuation rates associated with the four selected antiviral regimens for patients stratified by their status of previous treatment and HIV co-infection, the two factors having strong impact on treatment efficacy, treatment tolerance, and treatment decision making.

- *PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy*

The current revision has identified 35 trials comparing PEG/RBV-based triple therapy with boceprevir (9 trials), telaprevir (22 trials), or faldaprevir (4 trials) against 24 or 48-week PEG-IFN/RBV.

  - *Treatment-naïve patients without HIV co-infection:* Of the 35 identified trials, 23 trials assessed PEG-IFN/RBV-based triple therapy in treatment-naïve patients without HIV co-infection (5 trials for boceprevir,[41-45] 15 trials for telaprevir,[46-60] and 3 trials for faldaprevir[61-63]). The patients in these 23 trials had an average age of 48 years (n=1,218, 95% CI 46 to 50 years), 57.5% of patients were male (n=5,204, 95% CI 53.7% to 61.2%), 98.3% of patients had viral genotype 1 (n=5,870, 95% CI 96.9% to 99.1%), 84.3% of patients (n=4,967, 95% CI 80.3% to 87.6%) had mild fibrosis (F_0 to F_2), and 13.9% of patients (n=5,523, 95% CI 10.9% to 17.6%) had advanced fibrosis (F_3 or F_4). The pooled estimates of SVR and AE-related treatment discontinuation rates associated with

PEG/RBV-based triple therapy were 70.0% (n=7,149, 95% CI 67.0% to 72.8%) and 12.7% (n=4,072, 95% CI 10.3% to15.4%), respectively. The pooled estimates of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV doublet were 45.5% (n=2,041, 95% CI 43.3% to 47.8%) and 8.7% (n=981, 95% CI 7% to 10.9%), respectively.

- *Treatment-naïve patients with HIV co-infection:* Of the identified 35 trials, three trials compared PEG-IFN/RBV-based triple therapy (1 trial for boceprevir [64] and 2 trials for telaprevir[65,66]) versus PEG-IFN/RBV in treatment-naïve patients with HIV co-infection. Two trials which were comprised of 71 patients with reported patient baseline characteristics, including age (mean 42 years) and proportions of male (73.1%, 95% CI 61.5% to 82.1%), viral genotype 1 (97.8%, 95% CI 87.3% to 99.7%), and mild fibrosis stage (84.7%, 95% CI 74.3% to 91.4%). The pooled estimates of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV-based triple therapy were 73.5% (n=171, 95% CI 64.4% to 80.9%) and 20.0% (n=64, 95% CI 11.9% to 31.6%). The pooled estimate of SVR rate associated with PEG-IFN/RBV was 37.1% (n=62, 95% CI 26% to 49.8%). These three trials did not report AE-related treatment discontinuation rate associated with PEG-IFN/RBV. Thus, the current revision has assumed that HIV co-infection has the similar impact on AE-related treatment discontinuation associated with PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy. The AE-related treatment discontinuation rate associated with PEG-IFN/RBV in treatment-naïve patients with HIV co-infection is estimated by multiplying the relative risk (RR) of AE-related treatment discontinuation associated with HIV co-infection for PEG-IFN/RBV-based triple therapy

by the AE-related treatment discontinuation rate associated with PEG-IFN/RBV in treatment-naïve patients without HIV co-infection.

- *Previously treated patients without HIV co-infection:* Of the identified 35 trials, 9 trials compared PEG-IFN/RBV-based triple therapy (4 trials for boceprevir,[67-70] 5 trials for telaprevir,[71-75] and 1 trial for faldaprevir[76]) against PEG-IFN/RBV in previously treated patients without HIV co-infection. The average age of patients in these 9 trials was 50 years (n=333, 95% CI 49 to 51 years), 66.8% of patients were male (n=2,980, 95% CI 64.4% to 69.2%), 97.0% of patients had viral genotype 1 (n=2,980, 95% CI 95.0% to 98.2%), and 74.0% of patients had mild fibrosis (n=1,048, 95% CI 68.7% to 78.6%). The pooled estimate of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV-based triple therapy in these patients were 53.8% (n=2,377, 95% CI 45.2% to 62.3%) and 16.6% (n=1,773, 95% CI 11.1% to 24.2%), respectively. Of these 9 trials, five trials reported the rates of SVR (n=382, 37.4%, 95% CI 32.2% to 42.8%) and AE-related treatment discontinuation (n=233, 10.1%, 6.8% to 14.7%) rates associated with PEG-IFN/RBV.

- *Previously treated patients with HIV co-infection:* One trial[77] compared PEG-IFN/RBV/telaprevir triple therapy against PEG-IFN/RBV in 31 previously treated patients with HIV co-infection. The average age of these patients was 50 years. The proportions of male, viral genotype 1, and mild fibrosis in these 31 patients were 88.9%, 97.0%, and 90.6%, respectively. The reported SVR rate associated with PEG-IFN/RBV-based triple therapy was 73.8% (95% CI 55.6% to 86.4%). This trial only included 8

patients receiving PEG-IFN/RBV and this sample size was too small to have enough power for reliable estimation. Additionally, the SVR rate in these 8 patients was 50%, which was higher than the SVR rate in treatment-naïve patients. This finding was against many other trials reporting less treatment response associated with HIV co-infection. Thus, the current revision disregards the reported SVR rate associated with PEG-IFN/RBV in this trial but assumes that HIV has the same impact on treatment efficacies of PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy. The RR of SVR associated with HIV co-infection in patients receiving PEG-IFN/RBV-based triple therapy is multiplied by the estimated SVR rate associated with PEG-IFN/RBV in previously treated patients without HIV to estimate SVR rate associated with PEG-IFN/RBV in previously treated patients with HIV co-infection. This trial did not report AE-related treatment discontinuation rates associated with the two antiviral regimens either and the current revision assumes that their AE-related treatment discontinuation rates remained the same as what were reported in previously treated patients without HIV co-infection.

- *Sofosbuvir-based doublets*

The current revision has identified three trials assessing sofosbuvir-based doublets with simeprevir,[78] ledipasvir,[79] or daclatasvir [80] in treatment-naïve or previously treated patients without HIV co-infection.

- *Treatment-naïve patients without HIV co-infection:* One trial reported on 100 patients with an average age of 54 years and a male gender proportion of 52.7%. The proportions of viral genotype 1 and advanced fibrosis stage among studied patients were 97.4% (n=139, 95% CI 92.9% to 99.1%) and 20.4% (n=130, 95% CI 12.9% to 30.8%),

respectively. The pooled rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublets in these patients were 94.6% (n=139, 88.5% to 97.6%) and 2.2% (n=100, 0.6% to 8.4%), respectively.

- *Previously treated patients without HIV co-infection:* One trial reported on 21 patients with an average age of 59 years and a male gender proportion of 61.9%. The proportions of viral genotype 1 and advanced fibrosis stage among studied patients were 97.1% (n=50, 95% CI 87.0% to 99.4%) and 14.3% (n=21, 95% CI 4.7% to 36.2%), respectively. The pooled rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublets in these patients were 95.4% (n=69, 86.6% to 98.5%) and 2.2% (n=100, 0.6% to 8.4%), respectively.

- *3D regimen plus RBV*

Two phase III trials assessed treatment efficacy and safety associated with 3D regimen plus RBV in treatment-naïve (SAPPHIRE-I) [25] and previously treated patients (SAPPHIRE-II),[81] respectively. The 3D regimen consists of a boosted protease inhibitor ABT-450/ritonavir, NS5A inhibitor ABT-267, and non-nucleoside polymerase inhibitor ABT-333. In the SAPPHIRE-I trial, 473 previously untreated adult, non-cirrhotic, and viral genotype 1 patients received 12 weeks of 3D regimen plus RBV treatment. The reported SVR and AE-related treatment discontinuation rates associated with 3D regimen plus RBV in these treatment-naïve patients were 96.2% and 0.6%, respectively. In the SAPPHIRE-II trial, 297 previously treated adult, non-cirrhotic, and viral genotype 1 patients received 12 weeks of 3D regimen plus RBV treatment. The reported SVR and AE-related treatment discontinuation rates in these previously treated patients were 96.3% and 1%, respectively.

The current revision has not identified any specific trials that evaluated sofosbuvir-based doublets and 3D regimen plus RBV in patients with HIV co-infection. Based on the recommendations from clinical experts and the working group, HIV co-infection was assumed to have the same impact on SVR and AE-related treatment discontinuation associated with the four selected antiviral regimens when estimating the rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublet and 3D regimen plus RBV in patients with HIV co-infection. The estimated SVR and AE-related treatment discontinuation rates associated with the four selected antiviral regimens are summarized in *Table 5.1 and 5.2, respectively.*

2.2.3. Predicting treatment patterns over the next five years

Physicians are expecting significant change of treatment patterns for CHC because of those highly effective and safe new antiviral regimens. In order to estimate treatment patterns in surviving claimants over the next five years, the current revision has conducted an on-line survey study to measure physician's preferences for treating current surviving claimants with the four selected antiviral regimens discussed in the section of 2.2.2. This survey study invited physicians treating HCV in Ontario to review summarized baseline characteristics of surviving claimants eligible for treatment *(Table 6.1)* and the summarized SVR and AE-related treatment discontinuation rates associated with selected antiviral regimens (*Table 5.1 and 5.2*) and then indicate their likelihood of treating compensation claimants in a 0-100 scale and their treatment choices from the four selected antiviral regimens. This survey study received ethics approval

from the University of Toronto in January 2014 (PROTOCOL REFERENCE #29616) and the survey contents are attached as *Appendix I* of this report.

This survey study contacted approximately 100 Ontario physicians drawn from directories posted by the Canadian Liver Foundation[82] for physicians treating HCV across Canada. 14 physicians gave their written consents to participate in this on-line survey. The likelihoods of treating treatment-naïve and previously treated claimants without HIV co-infection in these 14 physicians were highly comparable (87.5% vs. 91.0%). However, their preferences to treat treatment-naïve and previously treated claimants with HIV co-infection were reduced to 65.8% and 61.7%, respectively. None of these 14 physicians selected PEG-IFN/RBV to treat any types of claimants and small proportions of the surveyed physicians selected PEG-IFN/RBV-based triple therapy to treat claimants (7.1% to 14.3%). When treating naïve claimants without HIV co-infection, sofosbuvir-based doublets were associated with a higher rate of selection than 3D regimen plus RBV (50% vs. 35.7%). However, 3D regimen plus RBV had a higher rate of selection than sofosbuvir-based doublets when treating treatment-naïve claimants with HIV co-infection (66.7% vs. 25%) and previously treated claimants, irrespective of their status of HIV co-infection (without HIV co-infection: 57.1% vs. 35.7%; with HIV co-infection: 83.4% vs. 8.3%) . The results of this survey study are summarized in *Table 6.2.*

2.2.4. Stage-specific fibrosis progression

Previous revisions explicitly described the MMLE method to estimate specific fibrosis stage transition rates using claims data of non-hemophilic claimants without HIV co-infection.[83] The current revision has used the same method to estimate stage-specific fibrosis progression using

updated claims data for non-hemophilic claimants without HIV co-infection. The first blood transfusion date and the latest compensation level associated with non-hemophilic claimants are used to estimate HCV infection time. A Markov model is constructed to simulate fibrosis progression starting from F_0 with an initial set of annual stage-specific fibrosis transition probabilities (0.1 for all transitions between consecutive fibrosis stages). The Markov model is run with iterations and modifications on each stage-specific annual transition probability until the squared residual sum, which indicates the difference between the predicted and observed fibrosis stage distributions, is less than 0.000001. Because the number of non-hemophilic claimants without HIV co-infection in the current revision only increases slightly to 3863 from 3839 in the last revision, the estimates of annual stage-specific transition probabilities in these two revisions are highly comparable. Calibration is also performed to further improve matching between predicted and observed fibrosis stage distributions at the time of claim in the non-hemophilic claimants without HIV co-infection. Similar to what was estimated in the fourth revision, the calibrated annual fibrosis transition probability from F_0 to F_1 is still less than half of annual transition probabilities for fibrosis progression above F_1 in the current revision. The uncalibrated and calibrated annual stage-specific fibrosis transition probabilities in the current revision and the fourth revision are summarized in *Table 7*.

2.2.5. Prognosis of cirrhosis in compensation claimants

In order to further improve internal validity of model outputs, the current revision has used claims data directly to estimate the rates at which decompensated cirrhosis, HCC, liver transplant, and liver-related mortality occurred in claimants with a diagnosis of compensated cirrhosis. This

is another major change from the fourth and previous revisions which mainly relied on literature based estimates.

- *Annual risk of developing decompensated cirrhosis:* 98 non-HIV and treatment naïve claimants were identified and retrospectively followed up from their first diagnosis of compensated cirrhosis to August 31, 2013. The claimants were censored when HCC, decompensated cirrhosis, liver transplant, or death occurred prior to the end of follow-up. 64 claimants developed decompensated cirrhosis over an average follow-up time of 13.1 years. The estimate of annual transition probability of developing decompensated cirrhosis in these claimants was 0.078 (95% CI 0.073 to 0.083).
- *Annual risk of developing HCC:* 98 non-HIV and treatment-naïve claimants were identified and retrospectively followed up from their first diagnosis of decompensated cirrhosis to August 31, 2013. The claimants were censored when HCC, decompensated cirrhosis, liver transplant, or death occurred prior to the end of follow-up. HCC developed in 28 claimants over an average follow-up time of 13.1 years. The estimated annual transition probability of developing HCC in these claimants was 0.025 (95% CI 0.024 to 0.027). Because the risk of developing HCC associated with compensated cirrhosis and decompensated cirrhosis was considered comparable, this estimate on the risk of HCC associated with decompensated cirrhosis was also applied to compensation claimants with compensated cirrhosis in the model.
- *Annual risk of liver transplantation:* 515 claimants with decompensated cirrhosis and/or HCC were identified and retrospectively followed up from their first decompensated cirrhosis or HCC diagnosis to August 31, 2013. 21 claimants were reported to have liver transplantation over an average follow-up time of 10.3 years. The estimate of annual

probability of receiving liver transplantation in these claimants was 0.004 (95% CI 0.0039 to 0.0042).

- *Annual risk of mortality associated with decompensated cirrhosis:* 414 claimants with a diagnosis of decompensated cirrhosis only were identified and retrospectively followed up from their first decompensated cirrhosis diagnosis to August 31, 2013 for any death records. A total of 343 deaths were recorded over an average follow-up period of 10.7 years. The estimate of annual risk of mortality associated with decompensated cirrhosis in these claimants was 0.152 (95% CI 0.146 to 0.158).
- *Annual risk of mortality associated with HCC:* 130 claimants with HCC were identified and retrospectively followed up for any death records after their first HCC diagnosis. A total of 110 deaths were reported in these claimants over an average time of 9.3 years. The estimate of annual risk of mortality associated with HCC in these claimants was 0.182 (95% CI 0.169 to 0.198).
- *Risk of first-year mortality after liver transplantation:* 58 claimants receiving liver transplantation were identified and retrospectively followed up for one year after the reported liver transplantation. A total of 5 deaths were recorded during this period. The estimate of the first-year mortality after liver transplantation in these claimants was 0.086 (95% CI 0.037 to 0.186).
- *Annual risk of mortality associated with post-transplantation*: 53 claimants survived for more than one year after liver transplantation. A total of 24 deaths were recorded in these claimants over an average follow-up time of 15.1 years. The estimate of annual risk of mortality associated with post-transplant in these claimants was 0.039 (95% CI 0.036 to 0.043).

Most claims data-based estimates for the prognosis of cirrhosis are comparable with literature derived estimates except that the annual mortality risk associated with HCC (0.182 vs. 0.35) and first-year mortality associated with liver transplantation (0.086 vs. 0.146) in the compensation claimants were about half of literature-based estimates in the fourth revision. Additionally, the assumed risk of liver transplantation associated with liver-related complications in the fourth revision is 25 times of that observed in the claimants (0.1 vs. 0.004). Thus, using estimates based on claims data in the HCV prognostic model is expected to generate more accurate model outputs than using estimates derived or assumed in the fourth revision. The estimates of the prognosis of cirrhosis derived from claims data and the fourth revision are summarized in *Table 8*.

2.2.6. Non-liver-related mortality

The current revision classifies mortality as liver-related mortality and non-liver-related mortality in order to differentiate death causes in simulated claimants. Liver-related mortality is defined as the death associated with any liver-related complications, such as decompensated cirrhosis, HCC, liver transplantation, or post-transplant. Non-liver-related mortality is defined as the death occurs prior to the diagnosis of any liver-related complications. Thus, non-liver-related mortality is applied to the claimants who have viral clearance due to SVC or successful antiviral therapy and also applied to uncured claimants without developed compensated cirrhosis and/or HCC in the HCV prognostic model. Previous revisions directly used Canada life tables as the source for non-liver-related mortality in the compensation claimants because the health problems which required blood transfusion so long ago in compensation claimants were unlikely to still have a meaningful impact on life expectancy and because current care has made virus-free hemophilics

almost have the same life expectancy as general population. However, these two hypotheses have never been tested before using claims data. Thus, the current revision has estimated the following annual risks of non-liver-related mortality from a group of surviving non-HIV claimants with a compensation level below 6 as of January 1, 2003 to test the two hypotheses through the comparisons with the 2009 to 2011 Canada life tables (*Table 9.1*) .[84]

- *Annual risk of non-liver-related mortality in hemophilic claimants:* 728 hemophilic claimants (589 males and 139 females) met the inclusion criteria for the analysis. These claimants were stratified by the defined age strata (every 10 years from age 20 years to 70 years or above) and gender. A total of 24 non-liver-related deaths (19 males and 5 females) were recorded in these claimants over the 10-year follow-up from 2003 to 2013. The estimated annual risks of non-liver-related mortality associated with the six age stratas increased from 0 to 0.017 in male hemophilics and from 0 to 0.0127 in female hemophilics. When compared with the Canada life tables stratified by age and gender, male hemophilics have comparable annual risk of non-liver-related mortality with general male Canadians except those at age 30 to 39 who have doubled annual non-liver-related mortality rate (0.0029 vs. 0.0001). When compared to general female Canadians, the female hemophilics at ages 40 to 49 (0.0032 vs. 0.0013) and 50 to 59 (0.0062 vs. 0.0031) have doubled annual risk of non-liver-related mortality. However, the sample size of female hemophilics in each age stratum ranged from 10 to 39, which were unlikely to have enough power to generate a reliable estimate from a statistical perspective. Thus, the current revision has used annual non-liver-related mortality rates derived from male hemophilic claimants under the age of 70 years and the female Canada life table to simulate non-liver-related mortality for hemophilics in the HCV prognostic model. Additionally, the Canada life table for males has been used in the model to

simulate non-liver-related mortality in male hemophilics at ages 70 or above due to the lack of claims data for accurate estimations. The estimated annual risks of non-liver-related mortality for hemophilic claimants are summarized in *Table 9.2.*

- *Annual risk of non-liver-related mortality in non-hemophilic claimants:* 2,877 non-hemophilic claimants (1,407 males and 1,470 females) met the inclusion criteria for the analysis of their annual non-liver-related mortality rates. These claimants were further stratified by the defined age strata and gender for a retrospective 10-year follow-up from 2003 to 2013 to identify non-liver-related deaths. A total of 185 non-liver-related deaths (124 males and 61 females) were identified and included for the survival analyses in non-hemophilics. Similar to the mortality patterns in the Canadian general population, non-hemophilic claimants with older age and male gender had higher non-liver-related mortality. The annual risk of non-liver-related mortality associated with the six age strata increased from 0.0017 to 0.015 in male non-hemophilics and from 0 to 0.01 in female non-hemophilics. However, male non-hemophilics persistently had substantially higher annual non-liver-related morality rates than general Canadians with male gender (ages 20 to 29: 0.0017 vs. 0.0007; ages 30 to 39: 0.0023 vs. 0.0010; ages 40 to 49: 0.0063 vs. 0.0019; ages 50 to 59: 0.0079 vs. 0.0048) until their ages reached to 60 years. Female non-hemophilics at ages 30 to 59 also had higher annual non-liver-related mortality rates than general Canadians with female gender (ages 30 to 39: 0.0013 vs. 0.0006; ages 40 to 49: 0.0019 vs. 0.0013; ages 50 to 59: 0.0049 vs. 0.0031). The identified differences in annual non-liver-related mortality between non-hemophilics and general Canadians are considered substantial. Thus, the current revision has applied the estimated annual non-liver-related mortality rates from both male and female non-hemophilic claimants under the age of 70 years for model simulation. The

Canada life tables are only used to simulate non-liver-related mortality in non-hemophilic claimants with ages above 70 years because the claims data are unlikely to give reliable estimations for age 70 to 79, 80 to 89, and 90 or above in the HCV prognostic model. The estimated annual non-liver-related mortality rates derived from male and female non-hemophilic claimants are summarized in *Table 9.3.*

2.2.7. Model estimates from the fourth revision

Even though the current revision aims to further improve accuracy of model outputs by maximizing the use of claims data to estimate model variables, there are still some model variables that can't be derived from claims data due to small sample size and missing information. Thus, the current revision continues to use the following estimates derived from the literature review in the fourth revision.

- *Impact of HIV on disease progression:* About a quarter of surviving claimants with hemophilia have an HIV co-infection that has been proven to accelerate disease progression,[85] reduce treatment response to antiviral therapy,[86] and increase non-liver-related mortality.[87] The impact of HIV on the treatment efficacies of the selected four antiviral regimens in the updated treatment patterns has been described in Section 2.2.2. Because nearly all claimants with HIV co-infection have hemophilia and the onset of HCV in hemophilic claimants was difficult to determine the MMLE method can't be used to estimate stage-specific fibrosis progression rates in these claimants with HIV co-infection. The fourth revision[88] conducted a systematic review to estimate the RR (2.12, 95% CI 1.52 to 2.97) of cirrhosis associated with HIV co-infection by comparing 2,636 HIV/HCV co-infection patients with 4,970 HCV mono-infection patients identified from 27 HCV natural

history studies. The fourth revision multiplied this RR by the annual stage-specific fibrosis progression rates in claimants without HIV co-infection to simulate the fibrosis progression in claimants with HIV co-infection. The current revision continues to use this solution to simulate fibrosis progression and also prognosis of cirrhosis in the current surviving claimants with HIV co-infection in the model.

- *Impact of HIV on non-liver-related mortality:* the current revision is able to retrospectively follow 238 claimants with HIV co-infection for 10 years, from 2003 to 2013, to estimate annual non-liver-related mortality rates by age strata and gender. The male claimants in three age strata, ages 20 to 29, 30 to 39, and 40 to 49, have a sample size above 50 and the estimated annual mortality rates from these claimants are higher than hemophilic claimants without HIV co-infection as expected (ages 20 to 29: 0.0083 vs. 0; ages 30 to 39: 0.0036 vs. 0.0029; ages 40 to 49: 0.0051 vs. 0.0022) (*Table 10*). Thus, the estimated non-liver-related mortality rates from these three age strata are considered reliable and used in the model to simulate non-liver-related mortality for male HIV-infected claimants with ages 20 to 50 years. However, the current revision has to simulate non-liver-related morality in other claimants with HIV co-infection using the estimated excess mortality associated with HIV (RR 6.24) from a meta-analysis comparing 5,168 HIV negative hemophilics with 2,979 HIV positive hemophilics for all-cause mortality in the fourth revision.[88]
- *SVC in patients with CHC*: A number of studies investigating the natural history of CHC have reported occurrence of SVC in patients with CHC.[89] The fourth revision identified 21 published studies reporting SVC in patients with CHC. The weighted mean SVC rate in these 21 studies was 0.020 (95% CI, 0.013-0.027). The fourth revision further pooled the estimated SVC rates from the literature and the observed SVC rate in the compensation claimants to

estimate the annual incidence rate of SVC (0.017, 95% CI 0.011 to 0.022) for the HCV prognostic model. Additionally, the fourth revision suggested that the chance of SVC would be reduced in advanced fibrosis stage. Thus, the current revision follows the suggestions made in the fourth revision by applying 0.017 as the annual SVC rate associated with F_0 and F_1, 0.01 as the annual SVC rate associated with F_2, and 0.005 as the annual SVC rate associated with F_3 in the HCV prognostic model.

- *Risk of HCC associated with fibrosis stage prior to cirrhosis:* The fourth revision applied a small annual incidence rate of HCC to non-cirrhotic claimants because HCC was found to develop at an average annual rate of 2.1% in non-cirrhotic patients in Japan[90]. Because Japanese have the highest incidence rate in HCC in the world and the compensation claimants differ from Japanese patients in ethnicity and viral transmission route, the fourth revision adopted the assumption made on this variable in the 1998 model which applied 0.0001 as the annual HCC rate associated with moderate fibrosis and zero for mild fibrosis. The fourth revision converted these rates by assuming that F_0 was comparable with mild fibrosis and F_1 to F_2 were comparable with moderate fibrosis. The fourth revision further assumed the annual rate of HCC associated with F_3 stage as 0.001 because advanced fibrosis stage was expected to have a higher risk of HCC. Thus, the current revision has adopted the same estimates used in the fourth revision for the risk of HCC associated with non-cirrhotic claimants.

2.3. Model assumptions

Assumptions are often made in model studies due to simplifying model structure or the lack of evidence. The current revision has made the following assumptions with respect to model structure and variables:

- *Initial distribution of fibrosis stages:* Because the latest compensation level determinations were unlikely to be made exactly as of August 31, 2013, the current revision has assumed that the latest claimed compensation levels remained unchanged in order to estimate the initial distribution of fibrosis stages in the simulated claimants. Additionally, the matching relationship between compensation level and fibrosis stage does not differentiate F_1 and F_2 in claimants with a compensation level of 3. The current revision has assumed that F_1 stage and F_2 stage are evenly distributed when estimating the initial distribution of fibrosis stages. Finally, the current revision has assumed that the estimated treatment outcomes of previous treatment in surveyed claimants are applicable to all previously treated claimants when estimating initial proportions of claimants with viral clearance and claimants who failed with previous treatments.
- *Natural history of CHC:* Most assumptions made by the fourth revision for fibrosis progression were retained in the current revision. For example, the HCV prognostic model only allowed fibrosis to progress in one direction. As well, fibrosis progression was assumed to stop when SVC or SVR was achieved in claimants with a fibrosis stage prior to compensated cirrhosis. Because HCC and decompensated cirrhosis were still observed in cirrhotic patients who had underwent successful antiviral treatment,[91] the current revision has assumed that successful antiviral therapy would reduce the risk of developing decompensated cirrhosis or HCC by half in cirrhotic claimants. Additionally, the current revision has assumed that CHC wouldn't affect mortality in claimants without any liver-related

complications to reflect the fact that liver-related death typically occurs following the development of liver-related complications.[92] Finally, the liver-related mortality, defined as the mortality associated with decompensated cirrhosis, HCC, and post-transplant, was fixed value and could be lower than non-liver-related mortality when claimants reached old age associated with high non-liver-related mortality. Thus, the model in the current revision would replace liver-related mortality with non-liver-related mortality once age-specific non-liver-related mortality excessed liver-related mortality in claimants with decompensated cirrhosis, HCC, or post-transplant.

- *Treatment patterns:* The current revision has utilized treatment preference data from the surveyed physicians to simulate future treatment patterns over the next five years in claimants chronically infected with HCV. Because the updated treatment patterns have high treatment rate and the new antiviral treatments are highly effective, the current revision has assumed no repeated treatment in the simulated claimants. Additionally, the claimants with developed liver-related complications are assumed not to receive antiviral treatments because SVR has limited impact on the prognosis of liver-related complications.[93]

2.4. Model validation

Different from the fourth revision which compared predicted and observed initial distribution of disease stages in the simulated claimants for model validation, the current revision has validated the revised HCV prognostic model by comparing predicted and observed prognosis of non-hemophilic claimants over a 10-year period from 2003 to 2013. This approach first created the validation cohort by including non-hemophilic claimants who were alive in 2003, had no HIV co-infection, and were treatment naïve. The initial distribution of fibrosis stages in this validation

cohort was estimated through the propensity score method described in the Section of 2.2.1. The revised HCV prognostic model was applied with the estimated initial distribution of disease stages in the validation cohort and model estimates for non-hemophilics to generate model outputs within 10-year time horizon. The predicted and observed cumulative rates of liver-related complications (decompensated cirrhosis: 6.1% vs. 7.4%; HCC: 1.9% vs. 1.8%; 0.7% vs. 0.7%) and all-cause mortality (10.6% vs. 11.9%) in the validation cohort are highly comparable. However, some discrepancies have been observed between the predicted and observed cumulative rates of liver-related mortality (5.5% vs. 7.4%) and non-liver-related mortality (9.0% vs. 4.5%) during 10-year follow-up. Further comparing the predicted and observed proportions of disease stages in the surviving non-hemophilics in 2013 has shown highly comparable proportions of F_0 with negative HCV RNA (25.1% vs. 24.8%), compensated cirrhosis (6.3% vs. 3.8%), decompensated cirrhosis (2.2% vs. 1.5%), HCC (0.9% vs. 0.4%), and post-transplant (0.5% vs. 0.5%). The predicted and observed outcomes in this validation cohort are summarized in *Table 11.*

3. Model predictions for current surviving compensation claimants

The current revision has used the revised HCV prognostic model to create two working models, one for hemophilic claimants and the other for non-hemophilic claimants, by applying the initial distributions of health states in surviving hemophilic and non-hemophilic claimants as of August 31, 2013. The model variables used in the two working models are summarized in *Table 12.* The two working models filled with baseline values of model variables were run with 50,000 iterations to simulate transitions between health states in surviving hemophilic and non-

hemophilic claimants within a time horizon of 57 years from 2013 to 2070. The generated model outputs from the two working models are further analysed for the following model predictions.

3.1. Model predictions for the entire claimant cohort

The proportion of hemophilia in the surviving claimants as of August 31, 2013 has been used to weight the model outputs of hemophilic and non-hemophilic claimants when predicting long-term prognosis of the entire cohort of surviving claimants as of August 31, 2013. The sum of the weighted model outputs from the two working models is used to calculate cumulative rates of liver-related complications and mortality and proportions of disease stages in surviving claimants every 10 years starting from 2020. The cumulative rates of decompensated cirrhosis (from 3.3% to 12.1%), HCC (from 0.7% to 4.3%), and liver-related mortality (0% to 14.7%) in the simulated claimants are predicted to increase persistently from 2013 to 2070. Because the applied treatments in the model can cure most claimants and fibrosis stages prior to cirrhosis are expected to remain unchanged in cured claimants, the predicted proportions of non-cirrhotic stages in surviving claimants only increase slightly. However, the proportion of compensated cirrhosis in surviving claimants is predicted to decrease from 10.8% in 2013 to 1.4% because cured cirrhosis still progresses to decompensated cirrhosis and HCC in the model. Even though liver-related complications are usually associated with high mortality, the continuous progression of cured and uncured compensated cirrhosis can cause newly developed liver-related complications and slow down the declining proportions of liver-related complications in surviving claimants. The model outputs of the entire cohort of surviving claimants are summarized by the defined calendar years in *Table 13.1.*

3.2. Comparing hemophilics versus non-hemophilics for model outputs

Hemophilic claimants are expected to have poorer long-term prognosis than non-hemophilic claimants because the higher prevalence of advanced fibrosis stage, HIV co-infection, and male gender in hemophilic claimants can reduce treatment response and accelerate disease progression. The current revision has compared the model outputs of hemophilic and non-hemophilic claimants and further confirmed this hypothesis. By 2070, hemophilic claimants are predicted to have doubled cumulative rates of decompensated cirrhosis (20.7% vs. 9.5%), HCC (7.3% vs. 3.4%), and liver-related mortality (24.9% vs. 11.6%) when compared to non-hemophilic claimants. Because hemophilic claimants have much higher initial proportion of compensated cirrhosis than non-hemophilic claimants (18.1% vs. 8.6%), the predicted proportions of decompensated cirrhosis and HCC in surviving hemophilics remained two times higher than what are predicted in surviving non-hemophilic claimants until 2040 when the differences in the predicted proportion of compensated cirrhosis between surviving hemophilics and non-hemophilics start to decrease substantially due to the lack of progression from cured claimants with less advanced fibrosis stage. Additionally, the low liver transplantation rate applied in the HCV prognostic model has made the predicted cumulative rates of liver transplantation in hemophilics and non-hemophilics highly comparable but very small (1.0% vs. 0.9%). The model outputs of hemophilic and non-hemophilic claimants are summarized by the selected calendar years in *Table 13.2.*

4. Model outputs stratified by age

In order to help with future planning of compensation funds for current surviving claimants, the current revision has stratified surviving claimants by age strata starting at 20 years with 10-year

interval until 90 years or above for the comparisons of model outputs between hemophilic and non-hemophilic claimants.

4.1. Ages 20 to 29

In this age stratum, hemophilic claimants have a much higher initial proportion of cirrhosis than non-hemophilic claimants (16.8% vs. 9.9%). Thus, these hemophilic claimants are expected to have higher risks of developing liver-related complications and mortality. Additionally, the long life expectancy associated with this age stratum can further increase the occurrences of liver-related complications and mortality. Based on the model outputs by 2070 for these claimants, the predicted cumulative rates of decompensated cirrhosis (18.8% vs. 12.4%), HCC (6.7% vs. 4.9%), and liver-related mortality (23.5% vs. 15.5%) associated with hemophilics are 1.367 to 1.516 times what are predicted in non-hemophilics. The future proportion of compensated cirrhosis in surviving hemophilics is predicted to decline faster than that in non-hemophilics until the calendar year of 2040 when the two predicted proportions become comparable (5.7% vs. 4.3%). Thus, hemophilics and non-hemophilics will also have comparable proportions of liver-related complications after the calendar year of 2040 (decompensated cirrhosis: 0.7 to 2.9% vs. 0.7 to 1.6%; HCC: 0.3 to 1.0% vs. 0.3 to 0.7%; post-transplant: 0.2 to 0.4% vs. 0.3%). The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.1.*

4.2. Ages 30 to 39

Hemophilic claimants in this age stratum continue to have an almost doubled initial proportion of cirrhosis (17% vs. 9.7%) than non-hemophilics. Because this age stratum is associated with

shorter life expectancy than ages 20 to 29, the disease progression time will be shorter and the developments of liver-related complications and mortality in these claimants are also reduced slightly, irrespective of their hemophilic status. Thus, the predicted cumulative rates of decompensated cirrhosis (18.2% vs. 11.3%), HCC (6.1% vs. 4.5%), and liver-related mortality (22.5% vs. 14.4%) in 2070 in hemophilics are 1.356 to1.611 times what are predicted in non-hemophilics. The proportion of compensated cirrhosis in hemophilics is predicted to decline faster than that in non-hemophilics until the calendar year of 2050 when the two predicted proportions are comparable (3.7% vs. 3.1%). Thus, the proportions of liver-related complications in surviving hemophilics and non-hemophilics are predicted to be highly comparable after the calendar year of 2050 (decompensated cirrhosis: 1.3 to 1.8% vs. 1.1% to 1.8%; HCC: 0.6% vs. 0.4 to 0.5%; post-transplant: 0.3% vs. 0.2 to 0.3%). The model outputs for hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.2.*

4.3. Ages 40 to 49

This age stratum is associated with a higher initial proportion of cirrhosis than ages 30 to 39, irrespective of claimant's hemophilic status. Additionally, the initial proportions of decompensated cirrhosis in hemophilic and non-hemophilic claimants in this age stratum have increased to 4.1% and 1.6%, respectively. Even though this age stratum is associated with shorter life expectancy, the high initial proportions of advanced disease stages in these claimants are likely to drive up future occurrences of liver-related complications and mortality. Since the initial proportion of cirrhosis in hemophilics is still two times higher than that in non-hemophilics in this age stratum (23.2% vs. 12.1%), the predicted cumulative rates of decompensated cirrhosis (23.1% vs. 12.9%), HCC (8.3% vs. 5.0%), and liver-related mortality (28.2% vs. 16.5%) by 2070

in hemophilics continue to be substantially higher than what are predicted in non-hemophilics. The proportions of cirrhosis in surviving hemophilics and non-hemophilics are predicted to decline to comparable levels (4.6% vs. 3.2%) in the calendar year of 2050. Surviving hemophilics and non-hemophilics are predicted to have comparable proportions of liver-related complications after the calendar year of 2050 (decompensated cirrhosis: 2.6 to 3.4% vs. 1.6 to 1.9%; HCC: 0.8 to 1.8% vs. 0.7 to 1.4%; post-transplant: 0.5 to 0.8% vs. 0.5 to 0.7%). The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.3.*

4.4. Ages 50 to 59

The initial proportions of cirrhosis (24.9% vs. 12.7%) and liver-related complications (decompensated cirrhosis: 4.8% vs. 2.8%; HCC: 1.9% vs. 0.9%) continue to increase in both hemophilic and non-hemophilic claimants in this age stratum. The shorter life expectancy of claimants in this age stratum begins to demonstrate strong impact on the disease prognosis as the predicted cumulative rates of decompensated cirrhosis, HCC, and liver-related mortality associated with this age stratum start to fall. However, the nearly doubled initial proportions of liver-related complications associated with hemophilics continue to make the predicted cumulative rates of decompensated cirrhosis (22.4% vs. 12.3%), HCC (8.5% vs. 4.3%), and liver-related mortality (27.1% vs. 15.3%) in hemophilics 1.771 to 1.977 times of what are predicted in non-hemophilics in 2070. However, hemophilics are predicted to have lower cumulative rates of liver transplantation than non-hemophilics (0.5% vs. 1.2%) due to substantially higher initial proportion of liver transplantation in non-hemophilics (0.9% vs. 0%). Our model predictions also indicate that no claimants will survive to 2070, irrespective of

hemophilic status. The proportions of compensated cirrhosis in surviving hemophilics and non-hemophilics are predicted to decline to a comparable level in 2060. Therefore, hemophilics are predicted to have persistently higher proportions of decompensated cirrhosis (4.3 to 6.2% vs. 2.2 to 2.9%) and HCC (1.7 to 4.9% vs. 0.7 to 2.5%) than non-hemophilics from 2020 to 2060. The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.4*.

4.5. Ages 60 to 69

Hemophilic and non-hemophilic claimants in this age stratum have the highest initial proportions of cirrhosis (30.8% vs. 14.5%), decompensated cirrhosis (10.2% vs. 4.2%), HCC (0.9% vs. 1.0%), and post-transplant (2.8% vs. 1.4%) in the entire claimant cohort. Even though the short life expectancy associated with this age stratum means no claimants will survive to 2060, the high initial proportions of advanced disease stages are expected to drive the cumulative rates of liver-related complications and mortality to the highest in both hemophilic and non-hemophilic claimants. When compared with non-hemophilics in this age stratum, hemophilics continue to have doubled initial proportions of cirrhosis and liver-related complications. Consequently, hemophilics are also predicted to have nearly doubled lifetime cumulative rates of decompensated cirrhosis (24.2% vs. 12.0%), HCC (6.8% vs. 4.3%), liver transplantation (3.4% vs. 1.7%), and liver-related mortality (28.1% vs. 14.5%) relative to non-hemophilics. Additionally, the much higher initial proportions of cirrhosis and liver-related complications in hemophilics are likely to make hemophilics to have sustainably higher proportions of liver-related complications than non-hemophilics over their survival time (decompensated cirrhosis: 6.8 to 7.8% vs. 2.6 to 5.3%; HCC: 2.3 to 4.6% vs. 1.0 to 2.4%; post-transplant: 2.7 to 4.1% vs.

1.3 to 2.0%). The model outputs of hemophilics and non-hemophilics in this age stratum are summarized in *Table 14.5*.

4.6. Ages 70 to 79

The initial disease stages associated with hemophilics are far more advanced than the initial stages associated with non-hemophilics in this age stratum (cirrhosis: 27.1% vs. 7.8%; decompensated cirrhosis: 12.2% vs. 5.1%; HCC: 6.1% vs. 0.7%, liver transplantation: 2% vs. 0.5%). However, the life expectancy associated with this age stratum is much reduced and no claimants in this age stratum will survive to 2050. Thus, further disease progression beyond 2050 will be stopped accordingly and the lifetime cumulative rates of liver-related complications and mortality in both hemophilic and non-hemophilic claimants are predicted to drop substantially. However, the predicted lifetime cumulative rates of decompensated cirrhosis (18.8% vs. 8.9%), HCC (9.1% vs. 2.6%), liver transplantation (2.5% vs. 0.7%), and liver-related mortality (20.8% vs. 10.1%) in hemophilics continue to be much higher that what are predicted in non-hemophilics. The higher initial proportions of compensated cirrhosis and decompensated cirrhosis associated with hemophilics also make the predicted proportions of liver-related complications in surviving hemophilics sustainably higher than what are predicted in non-hemophilics over their survival time (decompensated cirrhosis: 5.7 to 8.8% vs. 3.1 to 4.3%; HCC: 3.5 to 5.0% vs. 1.1 to 2.0%; post-transplant: 2.3 to 3.0% vs. 0.5 to 0.9%). The model outputs of hemophilic and non-hemophilic claimants in this age strata are summarized in *Table 14.6*.

4.7. Ages 80 to 89

The initial proportions of cirrhosis (7.7% vs. 8.9%) and decompensated cirrhosis (4.2% vs. 3.1%) in hemophilics in this age stratum substantially drop to be comparable with the initial proportions of the two advanced disease stages in non-hemophilics. Thus, the two types of claimants are expected to have similar long-term prognosis in their short life expectancy. Both hemophilics and non-hemophilics in this age stratum are predicted to have no survivors by 2040. Hemophilics and non-hemophilics are predicted to have comparable lifetime cumulative risks of liver-related complications (decompensated cirrhosis: 5.2% vs. 4.7%; HCC: 0.8% vs. 1.6%; liver transplantation: 0.1% vs. 0.4%) and mortality (5.5% vs. 5.2%) and also have comparable proportions of liver-related complications (decompensated cirrhosis: 4.5 to 4.9% vs. 2.5 to 3.0%; HCC: 0.8 to 1.9% vs. 1.1 to 2.1%; post-transplant: 0.1 to 0.4% vs. 0.3 to 0.4%) over their survival time. The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.7.*

4.8. Age strata of 90 years and above

Both hemophilics and non-hemophilics in this age stratum have further dropping but more comparable initial proportion of cirrhosis (4.3% vs. 4.5%). Within the much shortened life expectancy associated with this age stratum, both hemophilics and non-hemophilics are predicted to have very few occurrences of liver-related complications (decompensated cirrhosis: 0.5% vs. 1.8%; HCC: 0.2% vs. 0.6%; liver transplantation: 0% vs. 0.5%) and mortality (0.6% vs. 1.9%) by 2030 when no more claimants are predicted to survive. Thus, hemophilics and non-hemophilics also have highly comparable but extremely low proportions of liver-related complications (decompensated cirrhosis: 1.1% vs. 1.2%; HCC: 0.4% vs. 0.7%; post-transplant: 0%

vs. 0.5%) in 2020, the only defined calendar year with surviving claimants. The model outputs of hemophilics and non-hemophilics in this age stratum are summarized in *Table 14.8.*

5. Comparing model outputs of the current revision and the fourth revision

In order to demonstrate impact of updated treatment pattern and model variables on the long-term prognosis of current surviving claimants, we have compared the model outputs of the current revision and the fourth revision in the defined calendar years from 2020 to 2070. Because claimants only receive PEG-IFN/RBV combination treatment in the fourth revision, about of half of claimants are expected to fail with this treatment and continue to progress to more advanced disease stage. Thus, the predicted cumulative rates of liver-related complications and mortality in the fourth revision increase much faster than what are predicted in the current revision which mainly uses sofosbuvir-based doublet and 3D regimen plus RBV treatments, which can cure most claimants and substantially improve the long-term prognosis of compensation claimants. For example, the cumulative rate of cirrhosis in the fourth revision are predicted to increase from 24.3% in 2020 to 38.5% in 2060 (absolute difference: 14.2%) while the current revision predicts an increase of 2.9% (from 16.9% to 19.8%) for the cumulative rate of cirrhosis during the same period. Similar trends are also found in the comparisons of cumulative rates of HCC, liver transplantation, and liver-related mortality predicted by the fourth revision and the current revision. By 2060, the predicted cumulative rates of cirrhosis (38.5% vs. 19.8%), HCC (10.5% vs. 4.3%), and liver-related mortality (24.0% vs. 14.4%) in the fourth revision are nearly two times what are predicted in the current revision. Because the fourth revision assumed a much higher annual risk of liver-transplantation than the current revision (0.1 vs. 0.0004), the predicted cumulative rate of liver transplantation in the fourth revision in 2060 is 4.7 times the prediction

in the current revision (4.2% vs. 0.9%). Less effective antiviral therapy used in the fourth revision also affects the distribution of disease stages in surviving claimants over their survival time. Different from the relatively stable proportion of cirrhosis from 2020 to 2060 in the fourth revision (11.6% to 16.2%), the predicted proportion of cirrhosis in the current revision declines gradually (9.7% to 2.1%) due to the lack of new progressions from less advanced fibrosis stage. Thus, the fourth revision has persistently higher proportions of decompensated cirrhosis (2.9 to 4.3% vs. 1.5 to 3.2%) and HCC (1 to 1.5% vs. 0.7 to 1.1%) than the current revision over time from 2020 to 2060. The assumed higher annual risk of liver transplantation in the fourth revision could further drive up the predicted proportion of post-transplant in the fourth revision (1.5 to 4.1% vs. 0.5 to 0.7%). The model outputs of the fourth revision and the current revision are summarized in *Table 15*.

6. Sensitivity analyses

The substantial differences in model outputs of the current revision and the fourth revision have suggested that the model outputs of compensation claimants could be highly sensitive to the updates made in the current revision. When compared with the fourth revision, the current revision has updated treatment patterns using new antiviral regimens over the next five years and model estimates for the prognosis of cirrhosis and non-liver-related mortality using claims data. Thus, we have performed the following sensitivity analyses to assess the impact of the main updates on model outputs of current surviving non-hemophilic claimants.

6.1. Data sources of estimates for the prognosis of cirrhosis: Literature review vs. Claims data

The estimates for the prognosis of cirrhosis in the fourth revision were derived from literature review of studies including HCV patients irrespective of viral transmission route. Thus, the literature-based estimates are expected to have better external validity but poorer internal validity as the compensation claimants acquired HCV only through blood transfusion or blood products. The current claims data contain over 5,000 approved claimants and a large number of claimants have been followed up for 16 years since the compensation cohort was created in 1998. Thus, the claims data are believed to have enough sample size and follow-up time to estimate their own prognosis of cirrhosis and improve internal validity of model outputs. We have compared literature-derived estimates in the fourth revision and estimates based on claims data for the prognosis of cirrhosis (*Table 16.1.*). The annual risk of mortality associated with HCC in compensation claimants is about half of the estimate derived from literature (0.182 vs. 0.35). The first-year mortality rate after liver transplantation in compensation claimants is also much lower than what has been reported from literature (0.086 vs. 0.146). The fourth revision made an assumption on the chance of liver transplantation associated with decompensated cirrhosis or HCC due to the lack of literature. However, this assumed estimate is 4.7 times of the rate of liver transplantation (0.1 vs. 0.004) truly observed in compensation claimants. Thus, the estimates derived from claims data are expected to reduce the occurrences of liver-related mortality and liver transplantation. Comparing model outputs based on the two difference data sources has confirmed substantially higher cumulative rate of liver transplantation associated with claims data in 2070 (3.2% vs. 0.9%). However, the estimates based on claims data are unable to reduce liver-related mortality likely due to very low occurrences of HCC. Thus, the model outputs based on these two data sources are highly comparable except more occurrences of liver transplantation due to the assumption made in the fourth revision. The model outputs of non-hemophilics using

estimates derived from literature or claims data for the prognosis of cirrhosis are summarized in *Table 16.2.*

6.2. Non-liver-related mortality: claim cohort vs. 2009 to 2011 Canada life tables

The current revision updated non-liver-related mortality by using claims data for the same purpose of improving the accuracy of model outputs because the comorbidities associated with blood transfusion or blood products could substantially reduce the life expectancy of compensation claimants. We have used the claims data to estimate annual risk of non-liver-related mortality in non-HIV claimants stratified by age, gender, and hemophilic status and compared them with the 2009 to 2011 Canada age- and gender-specific life tables (*Table 17.1*). The comparisons have demonstrated that annual non-liver-related mortality rates associated with both hemophilics (male: 0.00290) and non-hemophilics (male: 0.00233; female: 0.00133) at ages 30 to 39 were nearly two times of the annual mortality rates in general Canadians (male: 0.00111; female: 0.00058) within the same age range. Annual non-liver-related mortality rates associated with male non-hemophilics in ages 40 to 49 (0.00632) and ages 50 to 59 (0.00794) were 3.3 times and 1.6 times of the annual mortality rates for male Canadians in the same age strata (ages 40 to 49: 0.00240; ages 50 to 59: 0.00619). Thus, we have also performed the sensitivity analysis to compare model outputs based on different data sources for non-liver-related mortality, claims data vs. Canada life tables, for any meaningful changes. However, the model outputs are not sensitive to the identified differences in non-liver-related mortality between claimants and general Canadians as the generated model outputs are almost identical. The comparisons observed almost identical model predictions on cumulative rates of liver-related complications and proportions of disease stages in the selected calendar years from 2020 to 2070. Even though

the relative differences in annual non-liver-related mortality rates between some compensation claimants and general Canadians look large, the absolute differences in annual non-liver-related mortality rates between them are too small to cause any obvious changes of model outputs. The model outputs based on annual non-liver-related mortality rates derived from claims data and the Canada life tables for non-hemophilics are summarized in *Table 17.2*.

6.3. Treatment patterns: current revision vs. the fourth revision

Updating treatment patterns with information from new antiviral regimens served as the major revision of the HCV prognostic model in this report. In order to demonstrate the impact of updated treatment patterns on model predictions, we have compared the model outputs of non-hemophilic claimants using treatment patterns estimated in the fourth revision and the current revision for the HCV prognostic model. The treatment patterns estimated in the two revisions are different in both treatment rate and treatment efficacy. The overall treatment rate in the fourth revision was 43.6%, which is about half of the treatment rate derived from the treatment preference survey study in the current revision. PEG-IFN/RBV was the only antiviral regimen used in the fourth revision and the treatment efficacy of this antiviral regimen was only about half of sofosbuvir-based doublets or 3D regimen plus RBV, the two antiviral regimens functioned as the primary methods of treatment in the current revision of the model. The substantially increased treatment rate and treatment efficacy of antiviral regimens associated with the updated treatment patterns in the current revision were expected to provide a cure for most claimants with CHC and significantly improve long-term prognosis of compensation claimants. Comparing the model outputs based on the two treatment patterns demonstrates that the predicted cumulative rates of decompensated cirrhosis (9.5% vs. 19.7%), HCC (3.4% vs.

8.3%), and liver-related mortality (11.6% vs. 24.9%) associated with the updated treatment patterns in the current revision were less than half of the predictions associated with previous treatment patterns used in the fourth revision. Because the treatment patterns in the fourth revision are expected to cure about one-quarter of surviving claimants and uncured claimants will continue the progression to advanced disease stage, the predicted proportion of compensated cirrhosis associated with treatment patterns in the current revision declines much faster than the prediction associated with previous treatment patterns in the fourth revision. Consequently, the proportions of decompensated cirrhosis (5.9 to 6.7% vs. 0.8 to 2.1%), HCC (2.4 to 3.3% vs. 0.4 to 0.9%), and post-transplant (0.8 to 1.3% vs. 0.4 to 0.7%) in non-hemophilic claimants receiving treatment patterns used in the fourth revision are predicted to be persistently higher than the predictions associated with current treatment patterns over their future survival time. The model outputs based on the two treatment patterns for surviving non-hemophilic claimants are summarized in *Table 18*.

7. Overall uncertainty associated with model predictions

The estimates of model variables are associated with more or less uncertainty that can cause model outputs to vary. Uncertainty associated with model variables is usually indicated by 95% CI, which can be used to construct the distributions of model variables. When exploring over uncertainty associated with model outputs, the mean values of the model variables in the disease prognostic model are replaced with the constructed distributions of model variables to calculate 95% CI of model outputs.

The current revision used the abovementioned method to estimate uncertainty associated with the long-term prognosis of surviving compensation claimants as of August 31, 2013. Because the model variables in the HCV prognostic model are probability/proportion variables that are usually associated with beta distribution, we have constructed the distributions of model variables using their 95% CIs and the assumption of beta distribution. After replacing the baseline values of model variables with the constructed model distributions in the HCV prognostic model, two-order Monte Carlo simulation analysis with 1000 trials for the first order and 50,000 trials for the second order was performed to generate 1000 model outputs for surviving hemophilic and non-hemophilic claimants, respectively. In order to estimate 95% CI of model outputs for the entire claimant cohort, the initial proportion of hemophilia in the surviving claimants (23.1%) has been used to determine the number of model outputs randomly selected from the 1000 model outputs for hemophilics and non-hemophilics. Thus, 231 randomly selected model outputs for hemophilics and 769 randomly selected model outputs for non-hemophilics were pooled to create 1000 model outputs representing the distribution of model outputs for the entire claimant cohort. Based on these 1000 model outputs, the estimated 95% CIs of cumulative decompensated cirrhosis, HCC, and liver-related mortality rates by 2070 were 8.7 to 15.5%, 3.1 to 5.5%, and 11.0 to 18.4%, respectively. The 95% CIs of cumulative rates of liver-related complications and mortality in the selected calendar years are summarized in *Table 19*.

8. Implications of current revision on future indirect costs to claimants

The current revision has predicted that the future treatment patterns over the next five years could cure most claimants and substantially reduce liver-related complications, which are usually associated with significant consumptions of health resources and also indirect costs related to

patient time, caregiver time, and out-of-pocket costs. According to a large survey study measuring 738 outpatients living in the metropolitan area of Vancouver, British Columbia, the annual patient time costs, caregiver time costs, and out-of-pocket costs associated with viral clearance were $281, $31, and $427, respectively. These costs associated with viral clearance were substantially lower than the costs associated with non-cirrhotic patients and further lower when compared to those costs associated with cirrhosis.[94] _ENREF_1This study also reported the lowest unemployment rate associated with viral clearance. Thus, successful treatment in a high proportion of HCV infected individuals, as is forecast by this model, may substantially reduce societal costs due to morbidity-related work loss, and may substantially reduce out of pocket expenses associated with ongoing HCV infection.

The economic impact of model outputs on compensation claimants is an important consideration for compensation budget planning as most claimants would get rid of the virus and their compensation needs would be substantially reduced. If future estimations on indirect costs to compensation claimants are needed, this Canadian survey study can be used as the source for the reference of indirect costs needed in the HCV prognostic model. For example, the health states used to summarize the annual patient time costs, caregiver time costs, and out-of-pocket time costs in this survey study could be easily matched with the health states in the HCV prognostic model. The reported annual indirect costs associated with the classified health states (*Table 20*) could be directly applied to the HCV prognostic model except treatment costs, which was based on interferon-based treatment. The new treatments are believed to be associated with much less treatment costs (not including drug costs) than interferon-based treatment because the treatment time of new treatments will be reduced to 12 weeks, which is a quarter of treatment time often

needed for interferon-based treatments. Additionally, the interferon-free treatments will cause much less toxicity and reduce indirect costs associated with AE management. Because this survey study also performed multiple regression analyses to assess the relationship between patient baseline characteristics and annual patient and caregiver time costs and out-of-pocket costs (*Table 21*), the reported coefficients associated with patient demographics, virus clearance, and disease stages can be used to construct a formula to predict indirect costs associated with claimants during each model cycle. The same adjustment for indirect costs associated with treatment is also needed in this method in order to reflect the reduced treatment time and toxicity associated with new antiviral regimens used in the current revision.

9. Discussion

The emergence of highly effective antiviral regimens for CHC is expected to substantially alter current treatment patterns as well as significantly improve the long-term prognosis of patients with CHC. Thus, the current revision has primarily focused on updating treatment patterns with new antiviral regimens and revising model predictions for current surviving compensation claimants due to the changed treatment patterns. The current revision has conducted a survey to measure a physician's likelihood of treating claimants and their preferences on treatment options that include current standard treatment and also three new antiviral regimens that will be ready for Canadian patients within two years. The survey results based on data from 14 physicians suggest that they are willing to treat most claimants using the most recently developed antiviral regimens, sofosbuvir-based doublets and 3D antivirals, likely because they can provide a cure for nearly all patients and their expensive costs can be compensated.

When compared with the fourth revision that was conducted in 2010, the current revision predicts that the lifetime cumulative rates of liver-related complications and mortality can be reduced by half mainly due to greatly improved treatment rates and treatment efficacy associated with new treatments. Separate model predictions for claimants stratified by hemophilic status have further confirmed much poorer prognosis associated with hemophilic claimants mainly because of more advanced disease stages and a much higher prevalence of HIV co-infection in hemophilics. When compared with non-hemophilic claimants, hemophilic claimants are predicted to have doubled lifetime cumulative rates of decompensated cirrhosis, HCC, and liver-related mortality. Further comparisons of model outputs between hemophilics and non-hemophilics stratified by age suggest that the higher initial proportion of cirrhosis in hemophilics is the main factor driving up the occurrences of liver-related complications and mortality. Even though the new treatments can cure most claimants, the cured claimants with developed cirrhosis still have a certain risk of progressing to more advanced stages and continue to increase the risks of liver-related complications and mortality.

The MMWG on the current revision has taken several steps to improve the accuracy of model outputs. First, the current revision includes a survey of previously treated claimants to determine their treatment outcomes that have significant impact on long-term prognosis and also treatment pattern. The overall SVR rate among surveyed claimants was 57.8%, which was highly consistent with the reported SVR rate associated with previous standard antiviral therapy using the combination of PEG-IFN and RBV. We believe that treatment outcome patterns in these surveyed claimants are highly valid when used to estimate the initial proportions of treatment responders and non-responders needed by the HCV prognostic model. Second, the current

revision has fully taken into account the possible impact of HIV co-infection and previous treatment on physician treatment preference[95,96] when conducting the treatment pattern survey study. Additionally, the surveyed physicians were asked to give their treatment preferences according to the summarized baseline characteristics of current surviving claimants chronically infected with HCV. Because previous revisions used the treatment patterns data derived from published survey studies for general patients with HCV, the estimated treatment patterns specifically for claimants stratified by the status of HIV co-infection and previous treatment should have much improved internal validity when simulating the same type of claimants in the model. For example, the results of this survey study indicate that over 90% of the surveyed physicians are willing to treat claimants with new treatments which are highly effective and also highly expensive. We believe that this treatment rate will substantially drop if these new treatments cannot be reimbursed. Finally, the current revision has tried to further improve the accuracy of model outputs by estimating model variables using claims data. Previous revisions mainly estimated model variables from literature or assumptions. When compared with model variables for the prognosis of cirrhosis in the fourth revision, the estimates of some model variables derived from claims data were much lower. For example, the assumed annual risk of receiving liver transplantation in the fourth revision is 25 times of the estimate derived from claims data. Using this assumed estimate would increase lifetime cumulative liver transplantation rate by 356% from 0.9% to 3.2% in surviving non-hemophilic claimants. Because liver transplantation increases costs tremendously to both patients and health care system, the revised prediction of the rate of liver transplantation in the future is expected to have significant impact on future compensation budget planning.

The previous revision validated the natural history model through the comparisons of predicted and observed initial distribution of disease stages in the simulated claimants. In contrast, the current revision compared predicted and observed liver-related complications and mortality by following a group of non-hemophilic claimants for 10 years. The predicted and observed liver-related complications are well matched. However, the predicted cumulative liver-related mortality rate was lower than what was observed whereas the predicted non-liver-related mortality was much higher than what was observed. We suspect that recorded liver-related complications present in the claim cohort may be less advanced due to treatment received via the compensation program. The risk of liver-related mortality among the claimant cohort is likely to be less than predicted by the literature because the cohort has received treatment under the compensation plan that those in other studies did not get (presumably due to cost issues). However, the impact of this bias on model predictions should be significantly minimized because the updated treatment patterns are expected to cure the majority of claimants with CHC and the occurrences of liver-related complications will be substantially reduced. Because claims involving deaths not caused by HCV would not be eligible to receive compensation, non-liver-related mortality in compensation claimants may not be fully recorded. The missing information on non-liver-related mortality could make the predicted non-liver-related mortality higher than the recorded non-liver-related mortality in compensation claimants. Because the two types of bias associated with mortality can be neutralized by each other, the predicted and observed all-cause mortalities are comparable. Thus, we believe that the HCV prognostic model used in the current revision is valid and able to generate reliable model predictions on the long-term prognosis of current surviving compensation claimants.

The current revision has also performed sensitivity analysis to assess the changes of model outputs associated with the major revisions made in the HCV prognostic model. The major revisions include the updated treatment patterns with new antiviral regimens and using claims data to estimate model variables for the prognosis of cirrhosis and non-liver-related mortality. These sensitivity analyses have not detected any meaningful changes of model outputs when changing the data sources for the estimations on the prognosis of cirrhosis and non-liver-related mortality. The insensitivity of model outputs to estimates derived from claims data for the prognosis of cirrhosis can be explained by the updated treatment patterns that will cure most of patients and substantially reduce the risk of cirrhosis in the compensation claimants. Thus, the impact of the changes of model variables for the prognosis of cirrhosis is unlikely to be demonstrated in a small number of cirrhotic claimants. Another sensitivity analysis observed almost identical model outputs based on non-liver-related mortality derived from claims data and the latest Canada life tables. Even though the non-liver-related mortality associated with some compensation claimants has been confirmed to be relatively larger than general population, the absolute differences in non-liver-related mortality between them are too small to cause any obvious changes of model outputs. The final sensitivity analysis compared the model outputs based on previous treatment patterns used in the fourth revision and the updated treatment pattern in the current revision. Similar to the comparisons of model outputs in the fourth revision and the current revision, the model predictions on the lifetime risks of liver-related complications and mortality are decreased by half when the updated treatment patterns in the current revision are used. Thus, these performed sensitivity analyses have confirmed that the predicted improvements of long-term prognosis in the current surviving claimants are solely driven by the

updated treatment patterns that will cure over 80% of surviving claimants with HCV over the next five years.

The current revision also has several limitations that may affect model predictions. The efficacy of antiviral regimens represented in the treatment pattern data are based on randomized clinical trials identified via a comprehensive search of main medical databases as well as proceedings from top liver-related conferences. However, the identified clinical trials are unable to provide all estimates needed in the model. For example, we have to assume that HIV co-infection has the same impact on SVR rates associated with new antiviral regimens as that found in traditional PEG-IFN/RBV treatment due to the lack of trials assessing new antiviral treatments in patients with HIV co-infection. Additionally, the reported treatment efficacies associated with these new antiviral regimens are determined based on SVR at 12 weeks, which is only half the time conventionally used to assess SVR following treatment. Even though both Health Canada and US FDA accept SVR at 12 weeks as the main outcome measure to assess treatment efficacies of new antivirals, there is no clinical evidence confirming that SVR at 12 weeks represents a clinical cure. Thus, current model predictions may require further adjustment if SVR rates associated with new antiviral regimens change appreciably given longer follow-up. Finally, the current revision doesn't take into account the prognosis of small number of claimants (33 claimants, 0.86% of total surviving claimants as of August 31, 2013) who were categorized into compensation level 6 because of liver-unrelated complications, such as lymphoma (8 claimants), cryoglobulinemia (14 claimants), and glomerulonephritis (11 claimants). Because cryoglobulinemia and glomerulonephritis can be substantially improved after eradication of HCV,[97] the new treatment patterns could make their impact on model prediction totally ignorable.

Also, more and more convincing evidence suggest that successful antiviral therapy improves cure rate of HCV-related lymphoma.[98] We believe that this small group of patients only have modest effects on the future mortality of the compensation cohort.

In summary, the HCV prognostic model has been revised by including future treatment pattern data which takes into account new antiviral regimens that are likely to be available in Canada within the next two years. The much improved treatment rate and cure rate associated with sofosbuvir-based doublets and 3D antiviral regimen plus RBV would reduce the lifetime risks of liver-related complications and mortality by half in current surviving hemophilic and non-hemophilic claimants. Additionally, hemophilic claimants are predicted to continue to have a worse prognosis than non-hemophilic claimants likely due to a higher initial proportion of cirrhosis and HIV co-infection. Thus, future compensation funds are definitely needed to be adjusted by taking into account the changes of treatment patterns, expected reductions of liver-related complications and mortality, and reduced indirect costs to claimants due to substantially improved cure rate.

10. References

1. The hepatitis C prevention, support and research program: Health Canada Initiatives on hepatitis C. Health Canada. Can J Public Health 2000;9:S27-31
2. Remis RS, Hogg RS, Krahn MD, Preiksaitis JK, Sherman M, Palmer RWH. Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-92: Report to Health Canada; 1998.
3. Zou S, Tepper M, Giulivi A. Current status of hepatitis C in Canada. Can J Public Health 2000;91 Suppl 1:S10-15, S10-16.
4. Scully LJ, Mitchell S, Gill P. Clinical and epidemiologic characteristics of hepatitis C in a gastroenterology/hepatology practice in Ottawa. CMAJ 1993;148(7):1173-7.
5. Stevens CE, Taylor PE, Pindyck J, Choo QL, Bradley DW, Kuo G, et al. Epidemiology of hepatitis C virus. A preliminary study in volunteer blood donors. JAMA 1990;263:49-53.
6. Comeau P. Hepatitis C compensation may be extended. CMAJ 2005;172:25.

7. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855-865.
8. Wong JB. Interferon treatment for chronic hepatitis B or C infection: costs and effectiveness. Acta Gastroenterol Belg 1998;61:238-242.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update.Hepatology 2009;49(4):1335-74.
10. Venkatraman S, Bogen SL, Arasappan A, et al. Discovery of (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino] carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo [3.1.0]hexan-2(S)-carboxamide (SCH 503034), a selective, potent, orally bioavailable hepatitis C virus NS3 protease inhibitor: a potential therapeutic agent for the treatment of hepatitis C infection. J Med Chem. 2006; 49:6074–86.
11. Lin C, Kwong AD, Perni RB. Discovery and development of VX-950, a novel, covalent, and reversible inhibitor of hepatitis C virus NS3.4A serine protease. Infect Disord Drug Targets 2006; 6: 3-16.
12. Maylin S, Martinot-Peignoux M, Ripault MP, et al. Sustained virological response is associated with clearance of hepatitis C virus RNA and a decrease in hepatitis C virus antibody. Liver Int 2009;29(4):511-7.
13. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.Lancet 2010;376(9742):705-16.
14. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364(25):2405-16.
15. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364(13):1207-17.
16. McHutchison JG, Manns MP, Muir AJ, et al.Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362(14):1292-303.
17. RK Chaudhary, M Tepper, S Eisaadany, Paul R Gully.Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System. Can J Infect Dis 1999; 10(1): 53–56.
18. Lin TI, Lenz O, Fanning G, et al. In vitro activity and preclinical profile of TMC435350, a potent hepatitis C virus protease inhibitor. Antimicrob Agents Chemother 2009;53(4):1377-85.
19. Herbst DA Jr, Reddy KR. Sofosbuvir, a nucleotide polymerase inhibitor, for the treatment of chronic hepatitis C virus infection.Expert Opin Investig Drugs 2013;22(4):527-36.
20. Ira M. Jacobson, Reem H. Ghalib, Maribel Rodriguez-Torres, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. 2013 AASLD annual meeting.
21. Sulkowski MS, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alfa-2a and ribavirin in treatment-naïve patients with chronic genotype 1 HCV: SILEN-C1 trial.Hepatology 2013;57(6):2143-54.
22. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection.N Engl J Med (published online on April 11, 2014)
23. Afdhal N, Reddy KR, Nelson DR, et al.Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.N Engl J Med 2014;370(16):1483-93.
24. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al.Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection.N Engl J Med 2014;370(3):211-21.
25. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin.N Engl J Med 2014;370(17):1594-603.

26. Dore GJ. The changing therapeutic landscape for hepatitis C. Med J Aust. 2012;196:629-632.
27. Aleman S et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C–associated liver cirrhosis. Clin Infect Dis 2013; 57:230-6.
28. Franchini M, Mengoli C, Veneri D, Mazzi R, Lippi G, Cruciani M. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. J Antimicrob Chemother 2008;61(6):1191-200.
29. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352: 1426–32.
30. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958–65.
31. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. Am J Cardiol 2003;92:1447-1451.
32. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-2281.
33. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2011_victrelis_141556-eng.php
34. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm
35. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_incivek_142482-eng.php
36. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm256328.htm
37. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_sovaldi_165043-eng.php
38. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm
39. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_galexos_164021-eng.php
40. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377234.htm
41. Pearlman BL and Ehleben C. Hepatitis C Genotype 1 Virus With Low Viral Load and Rapid Virologic Response to Peginterferon/Ribavirin Obviates a Protease Inhibitor. Hepatology 2014;59(1): 71-77.
42. Poordad F, Bronowicki JP,Gordon SC, et al.Factors That Predict Response of Patients With Hepatitis C Virus Infection to Boceprevir.GASTROENTEROLOGY 2012;143:608–618
43. Kwo PY, Lawitz EJ, McCone J et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010; 376(9742): 705-716.
44. Lawitz E, Zeuzem S, Nyberg L, et al. Boceprevir(BOC) combined with peginterferon alfa 2b/ribavirin (P/RBV) in treatment-naïve chronic HCV genotype 1 patients with compensated cirrhosis: sustained virologic response(SVR) and safety subanalyses from the anemia management study.Hepatology 2012;56(4):216A.
45. Poordad F, McCone J, Bacon B, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection.New England Journal of Medicine 2011;364(13): 1195-1206.
46. Basu P,Siriki R,Shah N, et al.Telaprevir with adjusted dose of ribavirin in naïve CHC-G1:efficacy and treatment in CHC in hemodialys is population. target c(RCT). Journal of Hepatology 2013;58:S30-S31.
47. Basu P, Shah N, Farhat S, et al. Pegylated interferon alfa,nitazaxanide,telapravir and ribavirin in prior experienced chronic hepatitis C genotype 1 patients-a randomized placebo control clinical pilot trial(INTRIGUE-C). Hepatology 2012;56(4):1035A.

48. Horsmans Y, Brown Jr R, Buti M, et al.Safety and efficacy of twice daily versus every 8 hour telaprevir with peginterferon/ribavirin (pr) in patients with cirrhosis.Journal of Hepatology 2013;58:S338-S339.
49. Mathurin P, Sarrazin C,Reesink H,et al.Treatment with telaprevir-based therapy after exposure to PEG-IFN/RBV in the realize study: results from the phase iiib c219 rollover study. Journal of Hepatology 2013;58:S356-S357.
50. McHutchison J, Everson G, Gordon S, et al. Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection. New England Journal of Medicine 2009;360(18): 1827-1838.
51. Sherman K, Flamm S, Afdhal N, et al.Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection.New England Journal of Medicine 2011;365(11): 1014-1024.
52. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for Retreatment of HCV Infection. New England Journal of Medicine 2011;364(25): 2417-2428.
53. Buti M, Agarwal K, Horsmans Y, et al.Telaprevir Twice Daily Is Noninferior to Telaprevir Every 8 Hours for Patients With Chronic Hepatitis C.Gastroenterology 2014;146(3):744-753
54. Hézode C, Forestier N, Dusheiko G, et al.Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360:1839-1850.
55. Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan.J Hepatol 2012;56(1):78-84.
56. Benhamou Y, Moussalli J, Ratziu V, et al.Telaprevir Activity in Treatment-Naive Patients Infected Hepatitis C Virus Genotype 4: A Randomized Trial. Journal of Infectious Diseases 2013; 208(6): 1000-1007.
57. Foster G, Hezode C, Bronowicki J, et al.Telaprevir Alone or With Peginterferon and Ribavirin Reduces HCV RNA in Patients With Chronic Genotype 2 but Not Genotype 3 Infections. Gastroenterology 2011;141(3): 881-889.
58. Jacobson I, McHutchison J, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. New England Journal of Medicine 2011;364(25): 2405-2416.
59. Marcellin P, Forns X, Goeser T, et al.Telaprevir Is Effective Given Every 8 or 12 Hours With Ribavirin and Peginterferon Alfa-2a or-2b to Patients With Chronic Hepatitis C.Gastroenterology 2011;140(2): 459-468.
60. Rizzetto M, Andreone P, Colombo M, et al. ADVANCE study: Final results of the phase III trial with telaprevir in combination with PEG-IFN and RBV in treatment-naive genotype 1 HCV. Digestive and Liver Disease 2011;43: S69-S69.
61. Rockstroh J, Nelson M, Soriano V,et al. Startverso 4 phase III trial of faldaprevir plus peginterferon alfa-2a and ribavirin(PR) in patients with HIV and HCV genptype 1 coinfection:end of treatment response.Hepatology 2013;58(4):741A-742A.
62. Ferenci P, Asselah T, Foster G, et al.Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic hcv genotype-1 treatment-na¨ive patients: final results from startverso1, a randomised, double-blind, placebo-controlled phase iii trial. Journal of Hepatology 2013; 58:S569–570.
63. Sulkowski M, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alfa-2a and ribavirin in treatment-naive patients with chronic genotype1 HCV: SILEN-C1 trial. Hepatology 2013;57(6): 2143-2154.
64. Sulkowski M, Pol S, Mallolas J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial.Lancet Infect Dis. 2013;13(7):597-605.
65. Sulkowski M, Sherman K, Dieterich D, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV A Randomized Trial. Annals of Internal Medicine 2013;159(2): 86-W35.
66. Sulkowski M, Sherman K, Soriano V,et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV co-infected patients:SVR24 final study results.Hepatology 2012; 56(4):219A-220A.

67. Poordad F, Bronowicki J, Gordon S, et al. Factors That Predict Response of Patients With Hepatitis C Virus Infection to Boceprevir. Gastroenterology 2012;143:608–618
68. Bacon B, Gordon S, Lawitz E, et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection.N Engl J Med 2011; 364(13): 1207–1217.
69. Hézode C, Fontaine H, Dorival C, et al.Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890.Journal of Hepatology 2013; 59:434–441
70. Flamm S, Lawitz E, Jacobson I, et al. Boceprevir With Peginterferon Alfa-2a–Ribavirin Is Effective for Previously Treated Chronic Hepatitis C Genotype 1 Infection.Clinical Gastroenterology and Hepatology 2013; 11:81–87
71. Pockros P, Zeuzem S, Lawitz E, et al.Telaprevir-Based Regimen in Genotype 1 Hepatitis C Virus-Infected Patients With Prior Null Response, Partial Response or Relapse to Peginterferon/Ribavirin: REALIZE Trial Final Results. Gastroenterology 2011;140(5): S898-S898.
72. Hayashi N, Okanoue T, Tsubouchi H, et al. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C.Journal of Viral Hepatitis 2012; 19:e134–e142.
73. Foster G, Zeuzem S, Andreone P, et al. Sustained virologic response rates with telaprevir by response after 4 weeks of lead-in therapy in patients with prior treatment failure. Journal of Hepatology 2013; 58:488–494.
74. Hézode C, Fontaine H, Dorival C, et al.Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890.Journal of Hepatology 2013; 59:434–441
75. McHutchison J, Manns M, Muir A, et al.Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010; 362(14):1292-303.
76. Sulkowski M, Bourliere M, Bronowicki J. et al.Faldaprevir combined with peginterferon alfa-2a and ribavirin in chronic hepatitis C virus genotype-1 patients with prior nonresponse: SILEN-C2 trial. Hepatology 2013;57(6): 2155-2163.
77. Sulkowski M, Sherman K, Dieterich D, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV A Randomized Trial. Annals of Internal Medicine 2013; 159(2): 86-W35.
78. Jacobson I, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: The COSMOS study.Hepatology 2013;58(6): 1379A-1380A.
79. Lawitz E, Poordad F, Pang P,et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial.Lancet. 2014;383(9916):515-23.
80. Sulkowski M, Gardiner D, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370(3):211-21.
81. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin.N Engl J Med 2014;370(17):1604-14.
82. http://liver.ca/liver-education-liver-research/resources-health-professionals/Physician_Directories.aspx
83. Yi Q, Wang PP, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. J Viral Hepat. 2004;11:166-174.
84. 2009 to 2011 Canada life tables. http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm
85. Mohsen AH, Easterbrook PJ, Taylor C, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut. 2003;52(7):1035-40.

86. Franchini M, Mengoli C, Veneri D, et tal. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. J Antimicrob Chemother 2008;61(6):1191-200.

87. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. Gut 2000;47(6):845-51.

88. Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990 (fourth revision)

89. Barrett S, Goh J, Coughlan B, Ryan E, Stewart S, Cockram A, O'Keane JC, Crowe J. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. Gut. 2001;49(3):423-30.

90. Yatsuhashi H, Yano M. Natural history of chronic hepatitis C. J Gastroenterol Hepatol 2000;15:E111-116.

91. Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13:5648-5653.

92. Ly KN, Xing J, Klevens RM, Jiles RB, Holmberg SD. Causes of death and characteristics of decedents with viral hepatitis, United States, 2010. Clin Infect Dis. 2014;58:40-49.

93. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis.Clin Ther. 2010;32(13):2117-38.

94. Federico CA, Hsu PC, Krajden M, et al. Patient time costs and out-of-pocket costs in hepatitis C. Liver Int. 2012;32:815-825.

95. Bova C, Ogawa LF, Sullivan-Bolyai S. Hepatitis C treatment experiences and decision making among patients living with HIV infection. J Assoc Nurses AIDS Care. 2010;21:63-74.

96. Niederau C, Huppe D, Zehnter E, et al. Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. World J Gastroenterol. 2012;18:1339-1347.

97. Alric L, Plaisier E, Thebault S, et al. Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. Am J Kidney Dis. 2004;43:617-623.

98. Takahashi K, Nishida N, Kawabata H, Haga H, Chiba T. Regression of Hodgkin lymphoma in response to antiviral therapy for hepatitis C virus infection. Intern Med. 2012;51:2745-2747.

11. Tables

Table 1. Baseline clinical and serological features of post-transfusion claimant cohort as of August 31, 2013: comparisons between hemophilics and non-hemophilics.

	Total	Hemophilics		non-Hemophilics		Statistical test	
Characteristics	N=5368	N=1345		N=4023			
	N	N	%*	N	%*	Chi	P
Sex							
Male	3303	1189	88.4	2114	52.5	547.423	*<0.001*
Female	2061	155	11.5	1906	47.4	547.815	*<0.001*
Missing	4	1	0.1	3	0.1	0.000	0.998

Survival status as of August 31, 2013							
Alive	3832	884	65.7	2948	73.3	27.789	***<0.001***
Dead	1536	461	34.3	1075	26.7	27.789	***<0.001***
Compensation level based on biopsy							
Yes	1053	232	17.3	821	20.4	6.378	***0.012***
No	4315	1113	82.7	3202	79.6	6.378	***0.012***
Level of compensation							
Level 1	872	155	11.5	717	17.8	29.390	***<0.001***
Level 2	1442	211	15.7	1231	30.6	114.078	***<0.001***
Level 3	1322	347	25.8	975	24.2	1.328	0.249
Level 4	292	84	6.3	208	5.2	2.265	0.132
Level 5	361	112	8.3	249	6.2	7.344	***0.007***
Level 6	610	148	11.0	462	11.5	0.231	0.631
Missing	469	288	21.4	181	4.5	361.636	***<0.001***
HCV therapy							
Yes	1342	378	28.1	964	24.0	9.223	***0.002***
No	4026	967	71.9	3059	76.0	9.223	***0.002***
HIV Positive							
Yes	537	412	30.6	125	3.1	848.248	***<0.001***
No	4339	847	63.0	3492	86.8	369.331	***<0.001***
Indeterminate	38	3	0.2	35	0.9	6.002	***0.014***
Missing	454	83	6.2	371	9.2	12.119	***0.001***
Age at first blood transfusion (yr)							
0-9	286	0	0.0	286	7.1	0.078	0.780
10-19	252	0	0.0	252	6.3	0.068	0.794
20-29	694	1	0.1	693	17.2	4.687	***0.030***
30-39	747	0	0.0	747	18.6	0.234	0.629
40-49	596	0	0.0	596	14.8	0.178	0.673
50-59	590	0	0.0	590	14.7	0.176	0.675
60-69	571	0	0.0	571	14.2	0.169	0.681
70+	203	0	0.0	203	5.1	0.054	0.816
Missing	7	0	0.0	7	0.2	0.002	0.966
Year at first blood transfusion							
<1986	567	0	0.0	567	14.1	0.168	0.682
1986	793	1	0.1	792	19.7	3.977	***0.046***
1987	805	0	0.0	805	20.0	0.256	0.613
1988	737	0	0.0	737	18.3	0.230	0.632
1989	751	0	0.0	751	18. 7	0.235	0.628
1990	292	0	0.0	292	7.3	0.080	0.777
Missing	1	0	0.0	1	0.0	0.000	0.987

Number of transfusions, 1986-1990							
1	1385	1	0.1	1384	34.4	1.850	0.174
2	348	0	0.0	348	8.7	0.097	0.756
3	183	0	0.0	183	4.6	0.049	0.825
4	272	0	0.0	272	6.8	0.074	0.786
5	100	0	0.0	100	2.5	0.026	0.872
>5	1653	0	0.0	1653	41.1	0.721	0.396
Missing	5	0	0.0	5	0.1	0.001	0.972
Among alive cohort	N=3832	N=884		N=2948			
HIV Positive							
Yes	326	227	25.7	99	3.4	435.296	***<0.001***
No	3160	595	67.3	2565	87.0	182.516	***<0.001***
Indeterminate	24	2	0.2	22	0.8	2.955	0.086
Missing	322	60	6.8	262	8.9	3.897	***0.048***
Sex							
Male	2173	749	84.7	1424	48.3	367.526	***<0.001***
Female	1655	134	15.2	1521	51.6	367.967	***<0.001***
Current age, mean (SD) years	5362	883	49.7 (13.7)	2944	61.8 (18.5)	17.970	***<0.001***

*Percentages were calculated based on available observations excluding missing and unknown categories.
HCV, hepatitis C virus; RNA, ribonucleic acid; SD, standard deviation.

Table 2.1. Baseline characteristics and SVR among previously treated compensation claimants.

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	118		354		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	118	51.3±10.7	354	57.0±13.7	***<0.001***
Male gender (%)	103	87.3	176	49.72	***<0.001***
Viral genotype (%)					
1a	34	28.8	95	26.8	0.721
1b	13	11.0	28	7.9	0.345

2 or 3	21	17.8	58	16.4	0.776
others	3	2.5	4	1.1	0.374
Unknown	47	39.8	169	47.7	0.165
Compensation level (%)					
2	21	17.8	42	11.9	0.118
3	41	34.8	196	55.4	***<0.001***
4	18	15.3	41	11.6	0.335
5	23	19.5	43	12.2	0.065
6	8	6.8	12	3.4	0.119
Unknown	7	5.9	20	5.7	1.000
HIV co-infection (%)	24	20.3	5	1.4	***<0.001***
Treatment outcome					
SVR (%)	55	46.6	218	61.6	***0.001***

SVR, sustained viral response; SD, standard deviation; HIV, human immunodeficiency virus

Table 2.2. Characteristics of surveyed compensation claimants with successful antiviral treatment (SVR).

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	55		218		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	55	50.0±11.2	218	56.1±14.0	***0.003***
Male gender (%)	49	89.1	109	50.0	***<0.001***
Viral genotype (%)					
1a	8	14.6	58	26.6	0.077

1b	7	12.7	12	5.5	0.075
2 or 3	13	23.6	40	18.4	0.445
others	2	3.6	3	1.4	0.265
Unknown	25	45.5	105	48.2	0.764
Compensation level (%)					
2	8	14.6	24	11.0	0.484
3	24	43.6	137	62.8	***0.014***
4	10	18.2	29	13.3	0.389
5	6	10.9	15	6.9	0.393
6	4	7.3	3	1.4	***0.032***
Unknown	3	5.5	10	4.6	0.729
HIV co-infection (%)	8	14.6	2	0.9	***<0.001***

Table 2.3. Characteristics of surveyed compensation claimants with unsuccessful antiviral treatment (no SVR).

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	62		119		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	62	52.5±10.2	119	58.4±13.1	***0.002***
Male gender (%)	53	85.5	60	50.4	***<0.001***
Vrial genotype (%)					
1a	26	41.9	35	29.4	0.1
1b	6	9.7	15	12.6	0.632

2 or 3	8	12.9	18	15.1	0.824
others	1	1.6	1	0.8	1
Unknown	21	33.9	50	42.0	0.337
Compensation level (%)					
2	12	19.4	17	14.3	0.398
3	17	27.4	48	40.3	0.103
4	8	12.9	11	9.2	0.453
5	17	27.4	25	21.0	0.357
6	4	6.5	8	6.7	1
Unknown	4	6.5	10	8.4	0.774
HIV co-infection (%)	16	25.8	2	1.7	***<0.001***

Table 3. Initial distribution of disease stages in the surviving compensation claimants stratified by their hemophilic status.

Hemophilic status			Hemophilics			Non-hemophilics		
Disease stage			Distribution (%)	initial age (years)	Male proportion (%)	Distribution (%)	initial age (years)	Male proportion (%)
SVC (level 1)			21.8	47.8	84.5	28.4	64.5	39.0
Responders to previous treatment	without HIV	level 2	2.7	41.4	89.3	2.0	59.8	46.0
		level 3	5.7	47.2	84.6	11.8	51.8	49.8
		level 4	3.5	49.0	83.2	2.4	59.7	41.2
		level 5	1.5	54.8	100.0	1.2	64.8	59.8
		missing	1.7	60.0	100.0	0.2	70.7	66.5
	with HIV	level 2	0.5	74.4	100.0	NA	NA	NA

		level 3	2.4	43.5	100.0	0.2	46.7	0.0
		level 4	0.0	NA	NA	NA	NA	NA
		level 5	0.3	49.0	100.0	NA	NA	NA
		missing	0.0	NA	NA	NA	NA	NA
Non-responders to previous treatment	Without HIV	level 2	2.8	50.1	68.6	1.4	63.6	64.8
		level 3	4.4	53.3	80.0	4.2	57.2	46.3
		level 4	1.6	52.1	100.0	0.9	61.8	55.1
		level 5	4.0	50.9	77.8	2.1	52.3	43.6
		missing	0.0	NA	NA	NA	NA	NA
		decompensated cirrhosis	0.9	48.9	100.0	0.6	57.2	72.8
		HCC	0.3	56.4	100.0	0.2	54.1	100.0
		post-transplant	0.0	NA	NA	0.1	64.4	0.0
	With HIV	level 2	1.1	63.3	100.0	NA	NA	NA
		level 3	1.5	50.2	100.0	NA	NA	NA
		level 4	0.9	45.6	100.0	NA	NA	NA
		level 5	1.2	54.8	100.0	NA	NA	NA
		missing	0.0	NA	NA	NA	NA	NA
		decompensated cirrhosis	0.5	36.5	100.0	NA	NA	NA
		HCC	0.0	NA	NA	NA	NA	NA
		post-transplant	0.0	NA	NA	NA	NA	NA
Treatment-naïve	without HIV	level 2	13.2	45.5	85.5	27.5	65.2	48.1
		level 3	10.0	59.0	73.9	11.7	60.4	47.1
		level 4	3.3	55.1	86.2	1.4	64.4	45.3
		level 5	1.6	50.9	85.7	2.0	71.1	53.4
		missing	0.1	79.1	100.0	NA	NA	NA
		decompensated cirrhosis	0.7	57.4	66.7	0.9	70.3	46.4
		HCC	0.3	52.8	100.0	0.2	72.5	60.0
		post-transplant	0.3	71.1	100.0	0.2	64.4	60.0
	with HIV	level 2	5.4	48.7	97.9	0.0	54.4	0.0
		level 3	3.8	44.2	100.0	NA	NA	NA
		level 4	0.6	46.0	100.0	0.0	50.9	100.0
		level 5	1.4	45.0	100.0	NA	NA	NA
		missing	0.1	71.5	100.0	NA	NA	NA
		decompensated cirrhosis	0.1	44.1	100.0	NA	NA	NA
		HCC	0.0	NA	NA	NA	NA	NA
		post-transplant	0.1	42.3	100.0	NA	NA	NA

SVC, spontaneous viral clearance; HIV, human immunodeficiency virus

Table 4.1. Estimated initial distribution of disease stages in surviving hemophilic claimants as of August 31, 2013.

Age strata	20 to 29		30 to 39		40 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 or above		All age	
Sample size	22		192		265		206		107		49		24		7		872	
Disease stage	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
F0, HCV RNA-	6	27.3	51	26.6	40	15.1	21	10.2	10	9.3	7	14.3	3	12.5	0	0.0	138	15.8
F0, HCV RNA+	4	18.2	38	19.8	48	18.1	39	18.9	14	13.1	12	24.5	16	66.7	6	85.7	177	20.3
F1/2	3.6	16.4	30.5	15.9	50.1	18.9	41	19.9	21.7	20.3	7.2	14.7	1.2	5.0	0.3	4.3	156	17.8
F3	4.7	21.4	39.7	20.7	65.3	24.6	53.5	26.0	28.3	26.4	9.4	19.2	1.6	6.7	0.4	5.7	203	23.3
F4, compensated cirrhosis	3.7	16.8	30.8	16.0	50.6	19.1	41.5	20.1	22	20.6	7.3	14.9	1.2	5.0	0.3	4.3	157	18.1
F4, decompensated cirrhosis	0	0.0	2	1.0	7	2.6	6	2.9	7	6.5	2	4.1	1	4.2	0	0.0	25	2.9
HCC	0	0.0	0	0.0	3	1.1	4	1.9	1	0.9	3	6.1	0	0.0	0	0.0	11	1.3
Post-transplant	0	0.0	0	0.0	1	0.4	0	0.0	3	2.8	1	2.0	0	0.0	0	0.0	5	0.6

Table 4.2. Estimated initial distribution of disease stages in surviving non-hemophilic claimants as of August 31, 2013.

Age strata	20 to 29		30 to 39		40 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 or above		All age	
Sample size	196		112		397		693		494		409		354		227		2882	
Disease stage	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
F0, HCV RNA-	31	15.8	23	20.5	71	17.9	128	18.5	77	15.6	70	17.1	67	18.9	38	16.7	505	17.5
F0, HCV RNA+	69	35.2	35	31.3	97	24.4	179	25.8	123	24.9	146	35.7	165	46.6	146	64.3	960	33.3
F1/2	54.7	27.9	30.8	27.5	129.8	32.7	213.6	30.8	158.9	32.2	100.1	24.5	64.6	18.2	23.3	10.3	775	26.9
F3	21.8	11.1	12.3	11.0	51.7	13.0	85.1	12.3	63.3	12.8	39.9	9.8	25.8	7.3	9.3	4.1	309	10.7
F4, compensated cirrhosis	17.5	8.9	9.9	8.8	41.5	10.5	68.3	9.9	50.8	10.3	32	7.8	20.6	5.8	7.4	3.3	248	8.6
F4, decompensated cirrhosis	1	0.5	1	0.9	3	0.8	11	1.6	9	1.8	16	3.9	7	2.0	1	0.4	49	1.7
HCC	0	0.0	0	0.0	1	0.3	2	0.3	5	1.0	3	0.7	3	0.8	1	0.4	15	0.5
Post-transplant	1	0.5	0	0.0	2	0.5	6	0.9	7	1.4	2	0.5	1	0.3	1	0.4	20	0.7

Table 5.1. Summary of synthesized SVR rates associated with selected four antiviral regimens in patients with CHC stratified by previous treatment status and HIV co-infection status.

Treatment regimen	Treatment duration	Treatment-naïve without HIV		Treatment-naïve with HIV		Previously treated without HIV		Previously treated with HIV	
		SVR	95% CI	SVR	95% CI	SVR	95% CI	SVR	95% CI
PEG-IFN/RBV	24 to 48 weeks	0.455	0.433 to 0.478	0.371	0.260 to 0.498	0.374	0.323 to 0.428	0.305	0.263 to 0.349
PEG-IFN/RBV-based triple therapy	24 to 48 weeks	0.7	0.670 to 0.728	0.735	0.644 to 0.809	0.538	0.452 to 0.623	0.538	0.452 to 0.623
Sofosbuvir-based doublet	12 weeks	0.946	0.885 to 0.976	0.802	0.751 to 0.828	0.954	0.866 to 0.985	0.809	0.734 to 0.783
3D regimen plus RBV	12 weeks	0.962	0.944 to 0.975	0.816	0.800 to 0.826	0.963	0.938 to 0.977	0.817	0.795 to 0.829

Table 5.2. Summary of synthesized AE-related treatment discontinuation rates associated with selected four antiviral regimens in patients with CHC stratified by previous treatment status and HIV co-infection status.

Anregimen	Treatment duration	Treatment-naïve without HIV		Treatment-naïve with HIV		Previously treated without HIV		Previously treated with HIV	
		Treatment discontinuation	95% CI	Treatment discontinuation	95% CI	Treatment discontinuation	95% CI	Treatment discontinuation	95% CI
PEG-IFN/RBV	24 to 48 weeks	0.1	0.05 to 0.16	0.18	0.02 to 0.33	0.131	0.07 to 0.21	0.236	0.126 to 0.378
PEG-IFN/RBV-based triple therapy	24 to 48 weeks	0.127	0.103 to 0.154	0.2	0.119 to 0.316	0.166	0.111 to 0.242	0.261	0.175 to 0.381
Sofosbuvir-based doublet	12 weeks	0.022	0.006 to 0.084	0.0396	0.011 to 0.151	0.022	0.006 to 0.084	0.0396	0.011 to 0.151
3D regimen plus RBV	12 weeks	0.006	0.001 to 0.018	0.0108	0.002 to 0.032	0.01	0.002 to 0.029	0.018	0.004 to 0.052

Table 6.1. Summary of baseline characteristics associated with surviving compensation claimants with ongoing CHC stratified by previous treatment status and HIV co-infection status.

Type of claimants	Treatment naïve without HIV	Treatment naïve without HIV	Previously treated without HIV	Previously treated with HIV
Age (years)	62.8 ± 20.2	47.6 ± 11.2	54.3 ± 14.0	50.2 ± 8.2
Male gender	53.3%	96.3%	58.0%	93.3%
Duration of HCV infection (years)	26.7 ± 4.8	25.0 ± 1.0	26.4 ± 5.2	26.0 ± 1.7
Hemophilics	16.2%	97.3%	27.3%	93.0%
Previous blood transfusion	81.9%	2.8%	71.4%	7.0%
Distribution of fibrosis stage				
F0	63.5%	39.4%	0.0%	0.0%
F1/F2	27.8%	39.4%	71.0%	53.5%
F3	3.8%	5.5%	15.2%	16.3%
F4	4.9%	15.6%	13.8%	30.2%
Distribution of viral genotype				
1	74.4%	75.0%	74.4%	75.0%
2 or 3	24.4%	16.7%	24.4%	16.7%
4, 5 or 6	1.2%	8.3%	1.3%	8.3%

Table 6.2. Summary of the treatment pattern based on 14 surveyed physicians for surviving compensation claimants with ongoing CHC over the next five years.

Treatment patterns	Treatment rate (%)		Treatment options							
			PEG/RBV		PEG/RBV-based triple therapy		Sofosbuvir-based doublet		3D regimen plus RBV	
Type of claimant	Baseline	95% CI	N	%	N	%	N	%	N	%
Treatment-naïve without HIV	87.5	79.2 to 95.8	0	0	2	14.3	7	50	5	35.7
Treatment-naïve with HIV	65.8	42.3 to 89.3	0	0	1	8.3	3	25	8	66.7
Previously treated without HIV	91.0	86.0 to 96.1	0	0	1	7.1	5	35.7	8	57.1
Previously treated with HIV	61.7	39.5 to 84.0	0	0	1	8.3	1	8.3	10	83.4

Table 7. Uncalibrated and calibrated annual stage-specific fibrosis transition probabilities derived from non-hemophilic claimants using MMLE method in the fourth and fifth revisions.

Revision version	Fibrosis transition	F0 to F1		F1 to F2		F2 to F3		F3 to F4	
		Baseline	95% CI	Baseline	95% CI	Baseline	95% CI	Baseline	95% CI
The fourth revision (2010)	Uncalibrated	0.029	0.025,0.032	0.118	0.080,0.145	0.137	0.079,0.175	0.103	0.042,0.130
	Calibrated	0.057	0.051,0.084	0.145	0.082,0.153	0.15	0.130,0.202	0.12	0.133,0.253
The fifth revision (2014)	Uncalibrated	0.038	0.033,0.044	0.101	0.074,0.128	0.133	0.084,0.182	0.114	0.063,0.166
	Calibrated	0.054	0.046,0.062	0.12	0.088,0.152	0.135	0.085,0.185	0.138	0.076,0.200

Table 8. Prognosis of cirrhosis derived from approved compensation claimants for the current revision and derived from literature in the fourth revision.

Transition between health states	Sample size	Cumulative events	Follow-up time (years)		Annual transition probability (fifth revision)		Annual transition probability (fourth revision)	
			Baseline	95% CI	Baseline	95% CI	Baseline	95% CI
Compensated cirrhosis to decompensated cirrhosis	98	64	13.05	12.22, 13.89	0.078	0.073,0.083	0.065	0.033,0.092
Compensated cirrhosis to HCC	98	28	13.05	12.22, 13.89	0.025	0.024,0.027	0.033	0.024,0.046
Decompensated cirrhosis to death	414	343	10.72	10.26, 11.19	0.152	0.146,0.158	0.186	0.137,0.250
HCC to death	130	110	9.32	8.50, 10.13	0.182	0.169,0.198	0.35	0.316,0.699
Decompensated cirrhosis or HCC to liver transplantation	515	21	10.29	9.87, 10.71	0.004	0.0039,0.0042	0.1	0.050,0.180
Mortality after liver transplantation (first year)	58	5			0.086	0.037,0.186	0.146	0.127,0.210
Mortality after liver transplantation (subsequent year)	53	24	15.06	13.73, 16.39	0.039	0.036,0.043	0.044	0.035,0.053

Table 9.1. Canadian age- and sex-related life table, 2009 to 2011.

Age	Male	Female	Age	Male	Female
1 year	0.0003	0.00021	56 years	0.00533	0.00336
2 years	0.00022	0.00016	57 years	0.00586	0.00368
3 years	0.00017	0.00013	58 years	0.00645	0.00403
4 years	0.00013	0.0001	59 years	0.00709	0.00442
5 years	0.00011	0.00009	60 years	0.0078	0.00485
6 years	0.0001	0.00008	61 years	0.00859	0.00533
7 years	0.00009	0.00007	62 years	0.00945	0.00586
8 years	0.00008	0.00007	63 years	0.0104	0.00645
9 years	0.00008	0.00007	64 years	0.01145	0.0071
10 years	0.00009	0.00008	65 years	0.0126	0.00782
11 years	0.0001	0.00008	66 years	0.01387	0.00862
12 years	0.00012	0.00009	67 years	0.01528	0.00951
13 years	0.00015	0.00011	68 years	0.01682	0.01051
14 years	0.0002	0.00014	69 years	0.01852	0.01161
15 years	0.00028	0.00018	70 years	0.0204	0.01284
16 years	0.00039	0.00022	71 years	0.02247	0.0142
17 years	0.00051	0.00026	72 years	0.02475	0.01573
18 years	0.00059	0.00028	73 years	0.02726	0.01743
19 years	0.00066	0.00029	74 years	0.03004	0.01934
20 years	0.00071	0.0003	75 years	0.0331	0.02146
21 years	0.00075	0.0003	76 years	0.03647	0.02384
22 years	0.00076	0.00031	77 years	0.04019	0.02649
23 years	0.00076	0.00031	78 years	0.0443	0.02947
24 years	0.00074	0.0003	79 years	0.04883	0.0328
25 years	0.00071	0.0003	80 years	0.05383	0.03654
26 years	0.0007	0.0003	81 years	0.05935	0.04074
27 years	0.00069	0.00031	82 years	0.06543	0.04545
28 years	0.0007	0.00032	83 years	0.07215	0.05074
29 years	0.00071	0.00034	84 years	0.07957	0.05669
30 years	0.00074	0.00037	85 years	0.08776	0.06338
31 years	0.00078	0.0004	86 years	0.0968	0.07091
32 years	0.00082	0.00043	87 years	0.10678	0.0794
33 years	0.00086	0.00047	88 years	0.1178	0.08897
34 years	0.00091	0.00051	89 years	0.12997	0.09977
35 years	0.00096	0.00056	90 years	0.14341	0.11196
36 years	0.00102	0.0006	91 years	0.15794	0.12542
37 years	0.00108	0.00066	92 years	0.17326	0.13991
38 years	0.00115	0.00071	93 years	0.18931	0.15541
39 years	0.00123	0.00077	94 years	0.20604	0.1719
40 years	0.00132	0.00084	95 years	0.21839	0.18849
41 years	0.00142	0.00092	96 years	0.23536	0.20653
42 years	0.00153	0.001	97 years	0.2529	0.22549
43 years	0.00165	0.00109	98 years	0.27092	0.24526
44 years	0.00179	0.00118	99 years	0.28933	0.26571
45 years	0.00194	0.00129	100 years	0.30802	0.28671
46 years	0.00211	0.0014	101 years	0.32687	0.3081
47 years	0.00229	0.00153	102 years	0.34576	0.3297
48 years	0.00251	0.00166	103 years	0.36457	0.35132
49 years	0.00275	0.00181	104 years	0.38319	0.3728
50 years	0.00301	0.00197	105 years	0.40149	0.39395
51 years	0.00331	0.00215	106 years	0.41937	0.41461
52 years	0.00364	0.00235	107 years	0.43673	0.43462
53 years	0.00401	0.00257	108 years	0.4535	0.45386
54 years	0.00441	0.0028	109 years	0.4696	0.47222
55 years	0.00484	0.00307	110 years and over	1	1

Table 9.2. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of hemophilic claimants stratified by age strata and gender.

Gender	Males			Females		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	139	0	0.0000	14	0	0.0000
30 to 39	170	5	0.0029	39	0	0.0000
40 to 49	133	3	0.0022	31	1	0.0032
50 to 59	70	3	0.0046	32	2	0.0062
60 to 69	49	4	0.0093	13	1	0.0078
70+	28	4	0.0170	10	1	0.0127

Table 9.3. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of non-hemophilic claimants stratified by age strata and gender.

Gender	Male			Female		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	59	1	0.0017	53	0	0.0000
30 to 39	217	5	0.0023	227	3	0.0013
40 to 49	293	18	0.0063	428	8	0.0019
50 to 59	248	19	0.0079	273	13	0.0049
60 to 69	238	30	0.0134	217	11	0.0052
70+	352	51	0.0155	272	26	0.0100

Table 10. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of claimants with HIV co-infection stratified by age strata and gender.

Gender	Male			Female		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	52	4	0.0083	0	0	-
30 to 39	89	3	0.0036	4	0	-
40 to 49	63	3	0.0051	3	0	-
50 to 59	18	0	-	0	0	-
60 to 69	3	0	-	1	0	-
70+	1	1	1	1	0	-

Table 11. Model predicted and observed prognosis of non-hemophilic claimants over 10-year follow-up from 2003 to 2013.

Outcome measure	2003 (observed)	2013 (observed)	2013 (predicted)
Cumulative rate (%)			
Cirrhosis	10.4	12.1	13.6
Decompensated cirrhosis	2.9	7.4	6.1
Liver transplantation	0.6	0.7	0.7
HCC	0.4	1.8	1.9
Liver-related mortality	0	7.4	4.1
Non-liver-related mortality	0	4.5	6.5
Proportion of disease stage among surviving claimants (%)			
F_0 with HCV RNA-	23.1	24.8	25.1
F_0 with HCV RNA+	46.9	46.7	29.3
F_1	6.8	10.2	19.7
F_2	6.8	10	9.1
F_3	5.9	2.2	7
Compensated cirrhosis	7.5	3.8	6.3
Decompensated cirrhosis	1.9	1.5	2.2
Post-transplant	0.6	0.5	0.5
HCC	0.4	0.4	0.9

Table 12. Summary of model variables applied to the HCV prognostic model in the current revision.

Model variables	Baseline value	Lower limit of 95% CI	Upper limit of 95% CI	Data source
Prevalence of hemophilia in the survival claim cohort on August 31, 2014	0.231			Table 1
Initial distribution of disease stage in survival hemophilia claimants				
F0 with HCV RNA-	0.158			Table 4.1
F0 with HCV RNA+	0.203			Table 4.1
F1/2	0.178			Table 4.1
F3	0.233			Table 4.1
F4, compensated cirrhosis	0.181			Table 4.1
F4, decompensated cirrhosis	0.029			Table 4.1
HCC	0.013			Table 4.1
Post-transplant	0.006			Table 4.1
Initial distribution of disease stage in survival non-hemophilia claimants				
F0 with HCV RNA-	0.175			Table 4.2
F0 with HCV RNA+	0.333			Table 4.2
F1/2	0.269			Table 4.2
F3	0.107			Table 4.2

F4 (compensated cirrhosis)	0.086			Table 4.2
Decompensated cirrhosis	0.017			Table 4.2
HCC	0.005			Table 4.2
Post-transplant	0.007			Table 4.2
Natural history of CHC				
Annual incidence rate of SVC for F0 and F1	0.017	0.011	0.022	The fourth revision report
Annual incidence rate of SVC for F2	0.01			The fourth revision report
Annual incidence rate of SVC for F3	0.005			The fourth revision report
Annual transition from F0 to F1	0.054	0.046	0.062	Table 7
Annual transition from F1 to F2	0.12	0.088	0.152	Table 7
Annual transition from F2 to F3	0.135	0.085	0.185	Table 7
Annual transition from F3 to F4	0.138	0.076	0.200	Table 7
Annual transition between fibrosis stages in treatment naïve or previously treated claimants with SVR	0			Model assumption
Annual risk of decompensated cirrhosis associated with compensated cirrhosis	0.078	0.073	0.083	Table 8
Annual risk of decompensated cirrhosis associated with compensated cirrhosis after successful antiviral treatment	0.039			Model assumption
Annual risk of HCC associated with F1 to F2	0.0001			The fourth revision report
Annual risk of HCC associated with F3	0.001			The fourth revision report
Annual risk of HCC associated with compensated cirrhosis	0.025	0.024	0.027	Table 8
Annual risk of mortality associated with decompensated cirrhosis	0.152	0.146	0.158	Table 8
Annual risk of mortality associated with HCC	0.182	0.169	0.198	Table 8
Annual risk of liver transplantation associated with decompensated cirrhosis or HCC	0.004	0.004	0.004	Table 8
Risk of mortality in the first year after liver transplantation	0.086	0.037	0.186	Table 8
Annual risk of mortality in subsequent years after liver transplantation	0.039	0.036	0.043	Table 8
Proportion of previous treatments in hemophilic claimants	0.38			Claims data
Proportion of previous treatments in non-hemophilic claimants	0.29			Claims data
SVR rate of previous antiviral treatment in hemophilic claimants	0.466			Table 2.1
SVR rate of previous antiviral treatment in non-hemophilic claimants	0.616			Table 2.1
Treatment pattern				
Treatment rate in treatment-naïve claimants without HIV	0.875	0.792	0.958	Table 6.3
Treatment rate in treatment-naïve claimants with HIV	0.658	0.423	0.893	Table 6.3
Treatment rate in previously treated claimants without HIV	0.91	0.86	0.961	Table 6.3
Treatment rate in previously treated claimants with HIV	0.617	0.395	0.84	Table 6.3
Distribution of antiviral regimens used in treatment-naïve claimants without HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.143			Table 6.3
Sofosbuvir-based doublet	0.5			Table 6.3
3D regimen plus RBV	0.357			Table 6.3
Distribution of antiviral regimens used in treatment-naïve claimants with HIV				

PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.083			Table 6.3
Sofosbuvir-based doublet	0.250			Table 6.3
3D regimen plus RBV	0.667			Table 6.3
Distribution of antiviral regimens used in previously treated claimants without HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.071			Table 6.3
Sofosbuvir-based doublet	0.357			Table 6.3
3D regimen plus RBV	0.571			Table 6.3
Distribution of antiviral regimens used in previously treated claimants with HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.083			Table 6.3
Sofosbuvir-based doublet	0.083			Table 6.3
3D regimen plus RBV	0.834			Table 6.3
Treatment efficacy of antiviral regiments in treatment-naïve patients without HIV				
PEG-IFN/RBV	0.455	0.433	0.478	Table 6.1
PEG-IFN/RBV-based triple therapy	0.7	0.67	0.728	Table 6.1
Sofosbuvir-based doublet	0.946	0.885	0.976	Table 6.1
3D regimen plus RBV	0.962	0.944	0.975	Table 6.1
Treatment efficacy of antiviral regiments in treatment-naïve patients with HIV				
PEG-IFN/RBV	0.371	0.26	0.498	Table 6.1
PEG-IFN/RBV-based triple therapy	0.735	0.644	0.809	Table 6.1
Sofosbuvir-based doublet	0.802	0.751	0.828	Table 6.1
3D regimen plus RBV	0.816	0.8	0.826	Table 6.1
Treatment efficacy of antiviral regiments in previously treated patients without HIV				
PEG-IFN/RBV	0.374	0.323	0.428	Table 6.1
PEG-IFN/RBV-based triple therapy	0.538	0.452	0.623	Table 6.1
Sofosbuvir-based doublet	0.954	0.866	0.985	Table 6.1
3D regimen plus RBV	0.963	0.938	0.977	Table 6.1
Treatment efficacy of antiviral regiments in previously treated patients with HIV				
PEG-IFN/RBV	0.305	0.263	0.349	Table 6.1
PEG-IFN/RBV-based triple therapy	0.538	0.452	0.623	Table 6.1
Sofosbuvir-based doublet	0.809	0.734	0.783	Table 6.1
3D regimen plus RBV	0.817	0.795	0.829	Table 6.1
Annual risk of non-liver-related mortality in male hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	0.003			Table 9.2
40 to 49	0.002			Table 9.2
50 to 59	0.005			Table 9.2
60 to 69	0.009			Table 9.2
70+	Canadian life table			Table 9.1

Annual risk of non-liver-related mortality in female hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	Canadian life table			Table 9.1
40 to 49	Canadian life table			Table 9.1
50 to 59	Canadian life table			Table 9.1
60 to 69	Canadian life table			Table 9.1
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in male non-hemophilics				
20 to 29	0.002			Table 9.3
30 to 39	0.002			Table 9.3
40 to 49	0.006			Table 9.3
50 to 59	0.008			Table 9.3
60 to 69	0.013			Table 9.3
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in female non-hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	0.001			Table 9.3
40 to 49	0.002			Table 9.3
50 to 59	0.005			Table 9.3
60 to 69	0.005			Table 9.3
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in male claimants with HIV co-infection				
20 to 29	0.0083			Table 10
30 to 39	0.0036			Table 10
40 to 49	0.0051			Table 10
RR of fibrosis progression associated with HIV co-infection	2.122	1.518	2.967	The fourth revision report
Excess mortality associated with HIV co-infection	6.24	5.43	7.18	The fourth revision report

Table 13.1. Model outputs by calendar year: All surviving claimants as of August 31, 2013.

Calendar year	2013	2020	2030	2040	2050	2060	2070

Cumulative proportion (%)*							
Cirrhosis	14.1	16.9	18.3	19.3	19.7	19.8	19.9
Decompensated cirrhosis	3.3	6.5	9.5	11.0	11.8	12.0	12.1
HCC	0.7	1.8	3.1	3.8	4.1	4.3	4.3
Liver transplantation	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality	0.0	14.9	32.6	48.5	63.5	75.1	81.2
Liver-related mortality	0.0	3.3	8.5	11.7	13.5	14.4	14.7
All-cause mortality	0.0	18.3	41.1	60.4	77.1	89.4	95.8
Sex distribution (%)							
Female	59.3	44.6	46.6	48.1	47.9	46.2	44.2
Age distribution (%)							
<30 yr	5.7						
30- yr	8.0	6.9					
40- yr	17.8	8.9	8.9				
50- yr	23.8	19.9	10.5	12.3			
60- yr	16.4	27.4	23.8	13.3	19.3		
70- yr	12.1	17.9	32.1	29.4	18.7	36.6	
80- yr	10.1	11.6	17.3	33.5	35.5	26.8	62.4
95- yr	6.1	7.5	7.3	11.4	26.5	36.5	37.6
Stage distribution (%)†							
F_0 with HCV RNA-	17.1	20.2	25.6	30.3	34.1	37.3	40.8
F_0 with HCV RNA+	30.3	25.1	20.7	18.0	15.7	13.6	10.8
F_1	12.4	13.8	14.1	14.0	14.4	14.7	15.2
F_2	12.4	12.7	13.4	13.6	13.9	14.2	14.5
F_3	13.6	13.6	14.6	15.2	15.3	15.3	15.6
Compensated cirrhosis	10.8	9.7	7.0	5.0	3.3	2.1	1.4
Decompensated cirrhosis	2.0	3.2	2.7	2.2	2.0	1.5	0.9
Post-transplant	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	0.7	1.1	1.1	1.0	0.8	0.7	0.5

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 13.2. Model outputs by calendar year: Hemophilics vs. Non-hemophilics.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	22.9	27.7	29.8	30.7	31.1	31.2	31.2	11.5	13.6	14.9	15.9	16.3	16.4	16.5
Decompensated cirrhosis	4.8	11.0	16.6	19.2	20.3	20.6	20.7	2.9	5.2	7.3	8.5	9.2	9.4	9.5
HCC	1.3	3.3	5.4	6.6	7.0	7.2	7.3	0.5	1.4	2.4	2.9	3.2	3.4	3.4
Liver transplantation	0.6	0.7	0.8	1.0	1.0	1.0	1.0	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		8.3	20.4	34.4	49.4	62.6	71.4		16.9	36.3	52.8	67.8	78.8	84.1
Liver-related mortality		5.5	14.9	20.5	23.2	24.5	24.9		2.7	6.6	9.1	10.6	11.3	11.6
All-cause mortality		13.8	35.2	54.9	72.6	87.1	96.3		19.6	42.9	62.0	78.5	90.1	95.6
Sex distribution (%)														
Female	84.8	15.8	16.3	16.2	16.0	16.2	14.4	51.6	53.3	55.7	57.7	57.5	55.2	53.2
Age distribution (%)														
<30 yr	2.5							6.6						
30- yr	21.7	2.7						3.9	8.1					
40- yr	31.0	23.3	3.1					13.8	4.5	10.7				
50- yr	23.5	32.3	26.2	3.8				23.9	16.2	5.8	14.8			
60- yr	12.3	24.2	35.1	31.4	5.4			17.6	28.3	20.4	7.9	23.5		
70- yr	5.6	11.9	24.0	39.1	40.9	9.2		14.1	19.7	34.6	26.5	12.0	44.8	
80- yr	2.7	4.2	9.5	20.4	41.2	54.9	20.1	12.3	13.8	19.6	37.5	33.8	18.4	75.1
95- yr	0.8	1.4	2.2	5.3	12.6	35.9	79.9	7.7	9.3	8.9	13.2	30.7	36.7	24.9
Stage distribution (%)†														
F_0 with HCV RNA-	15.8	18.9	23.8	28.0	31.1	33.7	34.8	17.5	20.6	26.2	31.0	35.0	38.4	42.6
F_0 with HCV RNA+	20.3	16.3	14.1	12.7	11.4	9.8	9.3	33.3	27.8	22.7	19.6	17.0	14.8	11.2
F_1	8.9	10.0	10.5	11.1	11.7	12.3	13.4	13.5	14.9	15.2	14.9	15.2	15.4	15.7
F_2	8.9	9.2	10.0	10.5	10.6	10.9	9.9	13.5	13.7	14.4	14.5	14.9	15.2	15.9
F_3	23.3	21.7	23.6	25.3	26.5	27.4	28.5	10.7	11.2	11.9	12.2	11.9	11.7	11.7
Cirrhosis	18.1	15.8	10.5	6.8	4.3	2.6	1.9	8.6	7.9	6.0	4.5	3.0	1.9	1.3
Decompensated cirrhosis	2.9	5.7	4.9	3.5	2.6	1.8	1.2	1.7	2.4	2.1	1.8	1.8	1.4	0.8
Post-transplant	0.6	0.6	0.6	0.7	0.7	0.7	0.4	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	1.3	1.9	1.8	1.5	1.1	0.9	0.7	0.5	0.8	0.9	0.8	0.7	0.6	0.4

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.1. Model outputs for claimants with ages 20 to 29.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	16.8	21.2	23.7	25.0	25.6	25.9	26.0	9.9	12.0	14.0	15.6	16.7	17.4	17.7
Decompensated cirrhosis		5.9	12.3	15.7	17.4	18.4	18.8	1.0	3.5	6.6	9.0	10.7	11.8	12.4
HCC		1.8	4.0	5.3	6.1	6.5	6.7	0	0.9	2.2	3.3	4.1	4.6	4.9
Liver transplantation		0.1	0.2	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.7	0.7	0.8	0.8
Non-liver-related mortality		0.9	5.6	9.4	15.4	24.7	42.8		0.7	2.8	6.6	11.9	19.1	36.3
Liver-related mortality		2.6	10.7	16.8	20.4	22.4	23.5		1.6	5.7	9.5	12.3	14.2	15.5
All-cause mortality		3.6	16.3	26.2	35.8	47.1	66.3		2.3	8.5	16.1	24.2	33.4	51.8
Alive	100	96.4	83.7	73.8	64.2	52.9	33.7	100	97.7	91.5	83.9	75.8	66.6	48.2
Stage distribution (%)†														
F_0 with HCV RNA-	27.3	29.4	34.3	38.9	42.5	44.7	46.5	15.8	19.5	25.0	29.8	34.1	37.6	40.9
F_0 with HCV RNA+	18.2	14.2	11.9	10.3	8.8	7.7	6.6	35.2	28.8	23.6	19.9	16.9	14.5	12.1
F_1	8.2	9.0	9.3	9.7	10.1	10.3	10.3	14.0	15.2	15.5	15.8	15.9	16.2	16.4
F_2	8.2	8.4	8.9	9.1	9.3	9.6	9.9	14.0	14.2	14.7	15.0	15.2	15.3	15.4
F_3	21.4	19.9	21.0	22.2	23.1	23.7	23.9	11.1	11.8	12.3	12.6	12.6	12.6	12.5
Compensated cirrhosis	16.8	14.1	9.1	5.7	3.6	2.3	1.5	8.9	7.8	5.8	4.3	3.0	2.0	1.3
Decompensated cirrhosis		3.8	4.1	2.9	1.7	1.0	0.7	0.5	1.9	1.9	1.6	1.3	1.0	0.7
Post-transplant		0.0	0.2	0.3	0.4	0.3	0.2	0.5	0.4	0.3	0.3	0.3	0.3	0.3
HCC		1.2	1.3	1.0	0.6	0.5	0.3	0	0.6	0.8	0.7	0.5	0.4	0.3

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.2. Model outputs for claimants with ages 30 to 39.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	17	21.2	23.5	24.7	25.3	25.6	25.6	9.7	11.7	13.7	15.2	16.3	16.7	16.9
Decompensated cirrhosis	1	6.7	12.5	15.7	17.3	18.0	18.2	0.9	3.2	6.3	8.6	10.1	11.0	11.3
HCC		1.7	3.7	4.9	5.6	6.0	6.1	0.0	1.0	2.2	3.1	3.8	4.3	4.5
Liver transplantation		0.1	0.2	0.4	0.4	0.5	0.5	0.0	0.0	0.1	0.2	0.3	0.3	0.3
Non-liver-related mortality		3.4	7.6	14.1	24.2	43.1	64.5	0.0	1.5	5.5	11.2	18.9	36.2	64.7
Liver-related mortality		3.1	11.0	16.6	19.9	21.6	22.5	0.0	1.7	5.6	9.0	11.7	13.5	14.4
All-cause mortality		6.5	18.6	30.7	44.1	64.7	87.0	0.0	3.2	11.1	20.3	30.6	49.7	79.1
Alive	100	93.5	81.4	69.3	55.9	35.3	13.1	100	96.8	88.9	79.7	69.4	50.3	20.9
Stage distribution (%)†														
F_0 with HCV RNA-	26.6	29.2	34.4	39.0	42.3	44.2	46.5	20.5	23.7	28.8	33.5	37.5	40.7	43.7
F_0 with HCV RNA+	19.8	15.7	13.1	11.4	10.1	8.9	7.4	31.3	25.6	20.9	17.5	14.8	12.6	10.5
F_1	7.9	9.1	9.3	9.5	9.9	9.9	9.7	13.8	14.7	14.8	15.0	15.3	15.6	15.5
F_2	7.9	8.1	8.6	8.8	9.0	9.2	9.1	13.8	14.2	14.7	14.8	15.0	15.0	14.7
F_3	20.7	19.2	20.4	21.6	22.4	23.1	23.6	11.0	11.6	12.0	12.3	12.2	12.4	12.4
Compensated cirrhosis	16	13.5	8.7	5.6	3.7	2.4	1.5	8.8	7.8	5.9	4.4	3.1	2.0	1.2
Decompensated cirrhosis	1	4.2	4.0	2.9	1.8	1.4	1.3	0.9	1.8	1.9	1.7	1.3	1.1	1.1
Post-transplant	0	0.1	0.2	0.3	0.3	0.3	0.3	0.0	0.0	0.1	0.2	0.2	0.2	0.3
HCC	0	1.0	1.3	0.9	0.6	0.6	0.6	0.0	0.6	0.7	0.7	0.5	0.4	0.5

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.3. Model outputs for claimants with ages 40 to 49.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	23.2	28.6	31.3	32.4	32.9	33.0	33.0	12.1	14.7	16.9	18.4	19.2	19.5	19.5
Decompensated cirrhosis	4.1	11.0	17.8	21.2	22.6	23.1	23.1	1.6	4.5	8.2	10.8	12.2	12.8	12.9
HCC	1.1	3.3	5.9	7.4	8.1	8.3	8.3	0.3	1.4	2.9	3.9	4.6	4.9	5.0
Liver transplantation	0.4	0.5	0.8	0.9	1.0	1.0	1.0	0.5	0.6	0.7	0.7	0.8	0.8	0.8
Non-liver-related mortality		3.0	10.0	20.1	38.3	59.2	70.7	0.0	2.7	8.3	15.7	33.6	62.2	81.4
Liver-related mortality		5.4	15.8	22.4	26.0	27.7	28.2	0.0	2.1	7.1	11.3	14.2	15.8	16.5
All-cause mortality		8.4	25.8	42.5	64.3	86.9	98.9	0.0	4.8	15.4	26.9	47.8	78.0	97.9
Alive	100	91.6	74.2	57.5	35.7	13.1	1.1	100	95.2	84.6	73.1	52.2	22.0	2.1
Stage distribution (%)†														
F_0 with HCV RNA-	15.1	18.0	22.6	26.5	29.4	31.7	33.9	17.9	20.6	25.1	29.1	32.4	34.9	33.9
F_0 with HCV RNA+	18.1	14.7	12.8	11.5	10.4	9.2	6.3	24.4	20.3	16.7	14.1	11.9	10.1	9.1
F_1	9.5	10.3	10.9	11.5	11.7	12.0	11.2	16.3	16.1	16.6	16.9	17.5	18.0	18.9
F_2	9.5	9.9	10.6	11.1	11.6	11.5	11.9	16.3	16.3	16.7	17.2	17.4	17.3	17.9
F_3	24.6	22.6	24.4	26.4	27.7	28.6	28.5	13.0	13.7	14.3	14.5	14.7	14.9	15.1
Compensated cirrhosis	19.1	16.7	11.2	7.2	4.6	2.8	2.3	10.5	9.4	6.8	4.8	3.2	2.0	1.1
Decompensated cirrhosis	2.6	5.6	5.0	3.8	2.8	2.6	3.4	0.8	2.3	2.5	2.1	1.7	1.6	1.9
Post-transplant	0.4	0.4	0.6	0.6	0.7	0.8	0.5	0.5	0.5	0.4	0.4	0.5	0.6	0.7
HCC	1.1	1.9	1.8	1.4	1.1	0.8	1.8	0.3	0.8	0.9	0.8	0.7	0.7	1.4

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.4. Model outputs for claimants with ages 50 to 59.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	24.9	31.0	33.5	34.3	34.6	34.6	34.6	12.7	15.2	17.2	18.5	19.1	19.2	19.2
Decompensated cirrhosis	4.8	12.0	18.6	21.3	22.3	22.4	22.4	2.8	5.6	9.0	11.1	12.1	12.3	12.3
HCC	1.9	4.3	6.7	7.9	8.4	8.5	8.5	0.3	1.3	2.8	3.7	4.2	4.3	4.3
Liver transplantation	0	0.1	0.3	0.4	0.5	0.5	0.5	0.9	0.9	1.1	1.1	1.2	1.2	1.2
Non-liver-related mortality		6.4	18.9	38.9	60.3	71.9	72.9	0.0	3.9	11.6	30.4	61.3	82.5	84.7
Liver-related mortality		6.4	16.9	23.2	25.9	27.0	27.1	0.0	2.7	7.6	11.6	14.1	15.1	15.3
All-cause mortality		12.8	35.9	62.1	86.3	98.9	100.0	0.0	6.6	19.2	41.9	75.4	97.6	100.0
Alive	100	87.2	64.1	37.9	13.7	1.1	0.0	100	93.4	80.8	58.1	24.6	2.4	0.0
Stage distribution (%)†														
F_0 with HCV RNA-	10.2	12.8	17.0	20.6	23.7	24.0	.	18.5	21.6	26.3	30.1	33.4	34.2	.
F_0 with HCV RNA+	18.9	15.3	13.4	12.2	10.6	9.6	.	25.8	21.7	17.9	15.3	12.9	9.1	.
F_1	10	10.9	11.6	12.0	12.7	10.7	.	15.4	15.4	15.9	16.4	16.9	19.0	.
F_2	10	10.4	11.2	11.8	12.3	11.8	.	15.4	15.4	15.8	16.1	15.8	15.4	.
F_3	26	23.9	26.1	28.1	28.4	29.5	.	12.3	12.9	13.4	13.6	13.7	12.8	.
Compensated cirrhosis	20.1	18.1	12.6	8.5	5.3	3.1	.	9.9	9.0	6.5	4.7	3.2	2.8	.
Decompensated cirrhosis	2.9	6.2	5.8	4.5	4.3	5.6	.	1.6	2.5	2.4	2.2	2.4	2.9	.
Post-transplant	0	0.1	0.3	0.5	0.6	0.7	.	0.9	0.7	0.7	0.8	0.9	1.4	.
HCC	1.9	2.3	2.0	1.7	2.0	4.9	.	0.3	0.7	0.9	0.9	0.8	2.5	.

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.5. Model outputs for claimants with ages 60 to 69.

Hemophilic status	Hemophilics							Non-hemophilics						
	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	30.8	36.8	38.6	39.0	39.1	39.1		14.5	16.9	18.9	19.8	19.9	19.9	
Decompensated cirrhosis	10.2	17.1	22.3	24.0	24.2	24.2		4.2	7.1	10.3	11.7	12.0	12.0	
HCC	0.9	3.5	5.8	6.6	6.7	6.8		1.0	2.1	3.5	4.2	4.3	4.3	
Liver transplantation	2.8	3.0	3.2	3.4	3.4	3.4		1.4	1.5	1.6	1.7	1.7	1.7	
Non-liver-related mortality		10.5	33.6	56.9	70.6	71.9		0.0	6.0	27.4	61.1	83.4	85.5	
Liver-related mortality		8.6	19.8	25.5	27.9	28.1		0.0	3.5	8.9	12.4	14.2	14.5	
All-cause mortality		19.1	53.4	82.4	98.4	100.0		0.0	9.5	36.3	73.5	97.6	100.0	
Alive	100	80.9	46.7	17.6	1.6	0.0		100	90.5	63.7	26.5	2.4	0.0	
Stage distribution (%)†														
F_0 with HCV RNA-	9.3	11.4	14.6	16.9	16.8	.	.	15.6	18.8	23.1	26.5	27.1	.	.
F_0 with HCV RNA+	13.1	11.3	10.2	8.9	8.5	.	.	24.9	20.7	17.4	14.3	12.0	.	.
F_1	10.1	10.1	11.0	11.3	12.6	.	.	16.1	16.2	16.5	16.7	17.1	.	.
F_2	10.1	10.6	11.4	12.4	11.4	.	.	16.1	16.3	16.7	16.4	16.9	.	.
F_3	26.4	24.9	27.1	29.0	29.8	.	.	12.8	13.9	14.3	14.9	14.2	.	.
Compensated cirrhosis	20.6	18.9	13.2	8.2	5.1	.	.	10.3	9.2	6.8	4.7	3.1	.	.
Decompensated cirrhosis	6.5	7.8	6.8	6.9	7.0	.	.	1.8	2.6	2.9	3.3	5.3	.	.
Post-transplant	2.8	2.7	3.1	3.5	4.1	.	.	1.4	1.3	1.3	1.6	2.0	.	.
HCC	0.9	2.3	2.7	2.7	4.6	.	.	1.0	1.0	1.1	1.5	2.4	.	.

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.6. Model outputs for claimants with ages 70 to 79.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	27.1	30.4	31.1	31.3	31.3			7.8	14.4	15.3	15.5	15.5		
Decompensated cirrhosis	12.2	16.2	18.5	18.8	18.8			5.1	7.0	8.5	8.8	8.9		
HCC	6.1	7.8	8.9	9.1	9.1			0.7	1.7	2.4	2.6	2.6		
Liver transplant	2	2.3	2.4	2.5	2.5			0.5	0.6	0.6	0.7	0.7		
Non-liver-related death		27.5	60.5	77.7	79.2			0.0	18.6	60.7	87.4	89.9		
Liver-related death		9.4	17.4	20.5	20.8			0.0	4.0	8.0	9.9	10.1		
All cause death		36.9	77.9	98.2	100.0			0.0	22.6	68.6	97.2	100.0		
Alive	100	63.1	22.1	1.8	0.0			100	77.4	31.4	2.8	0.0		
Stage distribution (%)†														
F0 RNA-	14.3	17.6	22.3	26.6	.	.	.	17.1	21.1	26.6	30.4	.		
F0 RNA+	24.5	20.7	17.3	13.5	.	.	.	35.7	30.3	24.6	20.4	.		
Fibrosis 1	7.4	9.1	9.6	10.0	.	.	.	12.2	14.0	14.0	13.4	.		
Fibrosis 2	7.4	8.0	8.5	8.5	.	.	.	12.2	12.8	13.2	13.9	.		
Fibrosis 3	19.2	18.5	20.0	19.5	.	.	.	9.8	10.3	11.1	11.3	.		
Compensated cirrhosis	14.9	13.4	9.0	5.2	.	.	.	7.8	6.9	5.1	3.5	.		
Decompensated cirrhosis	4.1	5.7	6.8	8.8	.	.	.	3.9	3.1	3.3	4.3	.		
Post-transplant	2	2.3	3.0	2.8	.	.	.	0.5	0.5	0.8	0.9	.		
HCC	6.1	4.5	3.5	5.0	.	.	.	0.7	1.1	1.2	2.0	.		

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.7. Model outputs for claimants with ages 80 to 89.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	7.7	9.5	9.6	9.7				8.9	9.7	9.9	9.9			
Decompensated cirrhosis	4.2	4.9	5.2	5.2				3.1	4.3	4.7	4.7			
HCC	0	0.5	0.7	0.8				0.8	1.4	1.6	1.6			
Liver transplantation	0	0.1	0.1	0.1				0.3	0.4	0.4	0.4			
Non-liver-related mortality		56.1	91.4	94.5				0.0	45.7	90.5	94.8			
Liver-related mortality		3.0	5.3	5.5				0.0	2.6	5.0	5.2			
All-cause mortality		59.0	96.6	100.0				0.0	48.4	95.5	100.0			
Alive	100	41.0	3.4	0.0				100	51.6	4.5	0.0			
Stage distribution (%)†														
F_0 with HCV RNA-	12.5	18.9	28.3	.	.	.	.	18.9	24.2	31.6	.			
F_0 with HCV RNA+	66.7	54.3	41.9	.	.	.	.	46.6	37.7	29.6	.			
F_1	2.5	7.5	8.3	.	.	.	.	9.1	12.1	12.6	.			
F_2	2.5	3.4	4.4	.	.	.	.	9.1	9.5	10.1	.			
F_3	6.7	6.6	6.4	.	.	.	.	7.3	7.7	7.6	.			
Compensated cirrhosis	5	4.0	3.3	.	.	.	.	5.8	4.7	3.0	.			
Decompensated cirrhosis	4.2	4.5	4.9	.	.	.	.	2.0	2.5	3.0	.			
Post-transplant	0	0.1	0.4	.	.	.	.	0.3	0.4	0.3	.			
HCC	0	0.8	1.9	.	.	.	.	0.8	1.1	2.1	.			

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.8. Model outputs for claimants with ages 90 or above.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	4.3	4.5	4.5					4.5	4.9	4.9				
Decompensated cirrhosis	0	0.4	0.5					1.2	1.7	1.8				
HCC	0	0.2	0.2					0.4	0.6	0.6				
Liver transplantation	0	0.0	0.0					0.4	0.5	0.5				
Non-liver-related mortality		86.9	99.4					0.0	80.9	98.1				
Liver-related mortality		0.4	0.6					0.0	1.4	1.9				
All-cause mortality		87.2	100.0					0.0	82.3	100.0				
Alive	100	12.8	0.0					100	17.7	0.0				
Stage distribution (%)†														
F_0 with HCV RNA-	0	8.5	.	.	.	.	.	16.7	23.4	.				
F_0 with HCV RNA+	85.7	69.2	.	.	.	.	.	64.3	51.4	.				
F_1	2.1	8.9	.	.	.	.	.	5.1	9.5	.				
F_2	2.1	3.2	.	.	.	.	.	5.1	5.9	.				
F_3	5.7	5.4	.	.	.	.	.	4.1	4.5	.				
Compensated cirrhosis	4.3	3.3	.	.	.	.	.	3.3	2.8	.				
Decompensated cirrhosis	0	1.1	.					0.4	1.2	.				
Post-transplant	0	0.0	.					0.4	0.5	.				
HCC	0	0.4	.					0.4	0.7	.				

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 15. Comparing model outputs for the fourth (2010) and current (2014) revisions.

Revision version	The fourth revision (2010)					The current revision (2014)				
Calendar year	2020	2030	2040	2050	2060	2020	2030	2040	2050	2060
Cumulative proportion (%)*										
Cirrhosis	24.3	32.2	36.3	37.9	38.5	16.9	18.3	19.3	19.7	19.8
HCC	4	7	9.1	10.1	10.5	1.8	3.1	3.8	4.1	4.3
Liver transplantation	2.9	3.6	3.9	4.1	4.2	0.7	0.8	0.9	0.9	0.9
Non-liver-related mortality	21.9	38.3	52.3	63.4	70.3	14.9	32.6	48.5	63.5	75.1
Liver-related mortality	7	14.6	20	22.8	24	3.3	8.5	11.7	13.5	14.4
All-cause mortality	29	52.9	72.2	86.3	94.3	18.3	41.1	60.4	77.1	89.4
Stage distribution (%)†										
F_0 with HCV RNA-	22.2	27.4	32.6	37.4	42	20.2	25.6	30.3	34.1	37.3
F_0 with HCV RNA+	15.8	8.4	4.5	2.4	1.3	25.1	20.7	18.0	15.7	13.6
F_1	12.2	10.3	9.2	9	8.2	13.8	14.1	14.0	14.4	14.7
F_2	13.2	12.3	11.8	11.8	11.8	12.7	13.4	13.6	13.9	14.2
F_3	16.4	17.1	16.8	16.7	17	13.6	14.6	15.2	15.3	15.3
Compensated cirrhosis	14.1	16.2	16.2	14.1	11.6	9.7	7.0	5.0	3.3	2.1
Decompensated cirrhosis	3.5	4.3	4.1	3.4	2.9	3.2	2.7	2.2	2.0	1.5
Post-transplant	1.5	2.5	3.2	3.9	4.1	0.7	0.7	0.6	0.6	0.5
HCC	1.2	1.5	1.5	1.3	1	1.1	1.1	1.0	0.8	0.7

Table 16.1. Comparing model estimates derived from claims data in the current revision and literature review in the fourth revision.

Data source	Claim cohort data based estimations			Literature based estimations		
Model variables (annual transition probability)	Baseline	95% CI		Baseline	95% CI	
Compensated cirrhosis to decompensated cirrhosis	0.078	0.073	0.083	0.065	0.033	0.092
Compensated cirrhosis to HCC	0.025	0.024	0.027	0.033	0.024	0.046
Decompensated cirrhosis to death	0.152	0.146	0.158	0.186	0.137	0.25
HCC to death	0.182	0.169	0.198	0.35	0.316	0.699
Decompensated cirrhosis or HCC to liver transplantation	0.004	0.004	0.004	0.1	0.05	0.18
First year mortality after liver transplantation	0.086	0.037	0.186	0.146	0.127	0.21
Subsequent year mortality after liver transplantation	0.039	0.036	0.043	0.044	0.035	0.053

Table 16.2. Comparing model outputs for non-hemophilic claimants using model variables derived from different data sources: Literature review vs. Claims data.

Model data source	Literature review							Claims data						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	11.5	13.3	14.7	15.5	16.0	16.1	16.2	11.5	13.6	14.9	15.9	16.3	16.4	16.5
Dec. Cirrhosis	2.9	4.7	6.5	7.6	8.1	8.3	8.4	2.9	5.2	7.3	8.5	9.2	9.4	9.5
HCC	0.5	1.6	2.6	3.3	3.6	3.7	3.8	0.5	1.4	2.4	2.9	3.2	3.4	3.4
Liver transplant	0.7	1.5	2.3	2.8	3.1	3.2	3.2	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		16.8	36.5	53.1	68.3	79.2	84.6		16.9	36.3	52.8	67.8	78.8	84.1
Liver-related mortality		3.1	6.4	8.6	10.0	10.8	11.1		2.7	6.6	9.1	10.6	11.3	11.6
All-cause mortality		19.9	42.9	61.7	78.3	89.9	95.7		19.6	42.9	62.0	78.5	90.1	95.6
Sex distribution (%)														
Female	48.4	53.9	56.6	58.4	58.9	55.9	53.6	51.6	53.3	55.7	57.7	57.5	55.2	53.2
Age distribution (%)														
<30 yr	6.6							6.6						
30- yr	3.9	8.1						3.9	8.1					
40- yr	13.8	4.6	10.7					13.8	4.5	10.7				
50- yr	23.9	16.0	5.9	14.8				23.9	16.2	5.8	14.8			
60- yr	17.6	28.4	20.1	7.9	23.4			17.6	28.3	20.4	7.9	23.5		
70- yr	14.1	19.8	34.8	26.2	12.2	44.7		14.1	19.7	34.6	26.5	12.0	44.8	
80- yr	12.3	13.6	19.7	37.7	33.7	18.9	75.5	12.3	13.8	19.6	37.5	33.8	18.4	75.1
95- yr	7.7	9.6	8.8	13.5	30.7	36.4	24.5	7.7	9.3	8.9	13.2	30.7	36.7	24.9
Stage distribution (%)†														
F_0 with HCV RNA-	17.5	21.2	26.5	31.1	34.8	38.8	42.8	17.5	20.6	26.2	31.0	35.0	38.4	42.6
F_0 with HCV RNA+	33.3	27.8	22.9	19.0	15.7	13.2	11.5	33.3	27.8	22.7	19.6	17.0	14.8	11.2
F_1	13.5	14.9	15.2	15.3	15.6	16.0	15.7	13.5	14.9	15.2	14.9	15.2	15.4	15.7
F_2	13.5	13.7	14.1	14.1	14.4	14.4	13.9	13.5	13.7	14.4	14.5	14.9	15.2	15.9
F_3	10.7	11.4	11.8	12.3	12.4	11.9	12.3	10.7	11.2	11.9	12.2	11.9	11.7	11.7
Compensated cirrhosis	8.6	7.9	6.1	4.5	3.4	2.0	1.3	8.6	7.9	6.0	4.5	3.0	1.9	1.3
Decompensated cirrhosis	1.7	1.4	1.0	0.8	0.8	0.6	0.2	1.7	2.4	2.1	1.8	1.8	1.4	0.8
Post-transplant	0.7	1.3	2.0	2.5	2.7	2.8	2.3	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	0.5	0.5	0.4	0.3	0.2	0.3	0.1	0.5	0.8	0.9	0.8	0.7	0.6	0.4

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, …).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 17.1. Estimates of non-liver-related mortality derived from the claimant cohort and the 2009 to 2011 Canada life tables.

Gender	Male			Female	
Age stratum	Hemophilics	Non-hemophilics	Canada life table	Non-hemophilics	Canada life table
20 to 29	0.00000	0.00171	0.00071	0.00000	0.00030
30 to 39	0.00290	0.00233	0.00096	0.00133	0.00056
40 to 49	0.00220	0.00632	0.00194	0.00189	0.00129
50 to 59	0.00464	0.00794	0.00484	0.00487	0.00307
60 to 69	0.00933	0.01338	0.01260	0.00519	0.00782

Table 17.2. Comparing model outputs for non-hemophilic claimants using non-liver-related mortality derived from different data sources: claims data vs. 2009 to 2011 Canada life tables.

Data source	Claims data							2009 to 2011 Canada life tables						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	11.5	13.6	14.9	15.9	16.3	16.4	16.5	11.5	13.1	14.5	15.4	15.8	16.0	16.0
Dec. Cirrhosis	2.9	5.2	7.3	8.5	9.2	9.4	9.5	2.9	5.1	7.3	8.6	9.2	9.4	9.5
HCC	0.5	1.4	2.4	2.9	3.2	3.4	3.4	0.5	1.4	2.3	2.9	3.2	3.3	3.4
Liver transplantation	0.7	0.7	0.8	0.9	0.9	0.9	0.9	0.7	0.8	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		16.9	36.3	52.8	67.8	78.8	84.1		16.6	35.8	52.3	67.2	78.5	84.1
Liver-related mortality		2.7	6.6	9.1	10.6	11.3	11.6		2.7	6.5	9.1	10.5	11.2	11.5
All-cause mortality		19.6	42.9	62.0	78.5	90.1	95.6		19.2	42.3	61.3	77.8	89.7	95.6
Sex distribution (%)														
Female	51.6	53.3	55.7	57.7	57.5	55.2	53.2	51.6	53.2	55.4	57.1	56.7	53.7	51.2
Age distribution (%)														
<30 yr	6.6		.	.	.	.	.	6.6						
30- yr	3.9	8.1						3.9	8.1	.	.	.	.	.
40- yr	13.8	4.5	10.7	.	.	.	.	13.8	4.6	10.7	.	.	.	.
50- yr	23.9	16.2	5.8	14.8	.	.	.	23.9	16.4	6.1	15.0	.	.	.
60- yr	17.6	28.3	20.4	7.9	23.5	.	.	17.6	28.7	20.9	8.3	24.3	.	.
70- yr	14.1	19.7	34.6	26.5	12.0	44.8	.	14.1	19.3	34.5	26.9	12.4	44.8	.
80- yr	12.3	13.8	19.6	37.5	33.8	18.4	75.1	12.3	13.5	19.4	37.1	33.6	19.1	76.6
95- yr	7.7	9.3	8.9	13.2	30.7	36.7	24.9	7.7	9.3	8.4	12.7	29.8	36.1	23.4
Stage distribution (%)†														
F_0 with HCV RNA-	17.5	20.6	26.2	31.0	35.0	38.4	42.6	17.5	20.7	26.4	31.2	35.1	38.3	40.6
F_0 with HCV RNA+	33.3	27.8	22.7	19.6	17.0	14.8	11.2	33.3	27.8	22.5	19.2	16.4	13.4	11.1
F_1	13.5	14.9	15.2	14.9	15.2	15.4	15.7	13.5	14.8	15.2	15.2	15.8	16.9	18.1
F_2	13.5	13.7	14.4	14.5	14.9	15.2	15.9	13.5	14.0	14.6	14.7	14.9	15.1	14.7
F_3	10.7	11.2	11.9	12.2	11.9	11.7	11.7	10.7	11.3	11.9	12.0	11.9	11.7	12.1
Compensated cirrhosis	8.6	7.9	6.0	4.5	3.0	1.9	1.3	8.6	7.4	5.7	4.2	3.1	2.2	1.5
Decompensated cirrhosis	1.7	2.4	2.1	1.8	1.8	1.4	0.8	1.7	2.5	2.2	2.0	1.6	1.4	1.0
Post-transplant	0.7	0.7	0.7	0.6	0.6	0.5	0.4	0.7	0.7	0.7	0.6	0.5	0.5	0.4
HCC	0.5	0.8	0.9	0.8	0.7	0.6	0.4	0.5	0.8	0.8	0.7	0.6	0.5	0.5

Table 18. Comparing model outputs for non-hemophilic claimants using treatment patterns in the current revision and the fourth revision.

Treatment pattern	The current revision in 2014						The fourth revision in 2010					
Calendar year	2020	2030	2040	2050	2060	2070	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*												
Cirrhosis	13.6	14.9	15.9	16.3	16.4	16.5	19.1	27.5	32.1	34.1	34.8	35.0
Dec. Cirrhosis	5.2	7.3	8.5	9.2	9.4	9.5	6.9	12.7	16.7	18.7	19.4	19.7
HCC	1.4	2.4	2.9	3.2	3.4	3.4	2.1	4.7	6.7	7.7	8.2	8.3
Liver transplantation	0.7	0.8	0.9	0.9	0.9	0.9	0.8	0.9	1.1	1.2	1.2	1.2
Non-liver-related mortality	16.9	36.3	52.8	67.8	78.8	84.1	16.8	34.9	48.8	60.3	68.1	71.8
Liver-related mortality	2.7	6.6	9.1	10.6	11.3	11.6	3.3	11.0	17.7	22.0	24.1	24.9
All-cause mortality	19.6	42.9	62.0	78.5	90.1	95.6	20.1	45.8	66.5	82.3	92.2	96.7
Sex distribution (%)												
Female	53.3	55.7	57.7	57.5	55.2	53.2	53.9	56.6	58.0	58.4	55.7	53.5
Age distribution (%)												
<30 yr		.	.	.	.	.						
30- yr	8.1						8.3	.	.	.	.	.
40- yr	4.5	10.7	.	.	.	.	4.7	10.8	.	.	.	.
50- yr	16.2	5.8	14.8	.	.	.	16.1	6.0	14.9	.	.	.
60- yr	28.3	20.4	7.9	23.5	.	.	27.8	20.2	8.1	23.5	.	.
70- yr	19.7	34.6	26.5	12.0	44.8	.	19.6	33.9	26.4	12.5	43.4	.
80- yr	13.8	19.6	37.5	33.8	18.4	75.1	13.7	19.5	36.9	33.0	19.2	72.1
95- yr	9.3	8.9	13.2	30.7	36.7	24.9	9.8	9.5	13.7	31.0	37.4	27.9
Stage distribution (%)†												
F_0 with HCV RNA-	20.6	26.2	31.0	35.0	38.4	42.6	20.9	25.8	30.7	34.6	36.8	39.1
F_0 with HCV RNA+	27.8	22.7	19.6	17.0	14.8	11.2	22.2	11.8	6.5	3.4	1.9	0.6
F_1	14.9	15.2	14.9	15.2	15.4	15.7	13.7	12.8	11.1	10.8	10.3	10.7
F_2	13.7	14.4	14.5	14.9	15.2	15.9	13.5	13.3	13.7	13.8	15.2	14.2
F_3	11.2	11.9	12.2	11.9	11.7	11.7	12.1	13.3	13.9	14.8	15.7	17.5
Compensated cirrhosis	7.9	6.0	4.5	3.0	1.9	1.3	11.6	13.9	13.4	11.7	10.1	7.7
Decompensated cirrhosis	2.4	2.1	1.8	1.8	1.4	0.8	3.9	5.9	6.7	6.5	6.0	6.3
Post-transplant	0.7	0.7	0.6	0.6	0.5	0.4	0.6	0.8	1.0	1.1	1.1	1.3
HCC	0.8	0.9	0.8	0.7	0.6	0.4	1.5	2.4	3.1	3.3	2.8	2.6

Table 19. Monte Carlo simulation projecting the 95% CI of the model predictions on cumulative rates of liver-related clinical outcomes.

Calendar year	2020		2030		2040		2050		2060		2070	
Cumulative rates of clinical outcomes (%)	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cirrhosis	16.9	14.6 -19.2	18.3	14.7 -21.9	19.3	15.0 -23.6	19.7	14.8 -24.6	19.8	14.6 -25.0	19.9	14.7 -25.1
Decompensated cirrhosis	6.5	5.5 -7.5	9.5	7.5 -11.5	11	8.4 -13.6	11.8	8.6 -15.0	12	8.7 -15.3	12.1	8.7 -15.5
HCC	1.8	1.4 -2.2	3.1	2.3 -3.9	3.8	2.8 -4.8	4.1	2.9 -5.3	4.3	3.1 -5.6	4.3	3.1 -5.5
Liver-related mortality	3.3	2.8 -3.8	8.5	7.0 -10.0	11.7	9.3 -14.1	13.5	10.3 -16.7	14.4	10.8 -18.0	14.7	11.0 -18.4

Table 20. Reported mean cost to HCV patients and their caregivers by disease stage in a recent Canadian survey study.

Disease stage	Patient time costs	Caregiver time costs	Out-of-pocket costs
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Chronic (N = 326)	$1411 ($931–1891)	$60 ($23–98)	$1150 ($615–1686)
Treatment (N = 61)	$1481 ($851–2111)	$152 ($18–285)	$2496 ($677–4316)
Viral clearance (N = 148)	$281 ($175–387)	$31 ($0–72)	$427 ($73–780)
Cirrhosis (N = 135)	$3588 ($1766–5411)	$766 ($173–1359)	$1667 ($766–2568)
HCC (N = 21)	$2739 ($972–4507)	$1050 ($45–2345)	$2837 ($178–5495)
Transplant (N = 47)	$9416 ($2987–15 844)	$2460 ($1–4982)	$2204 ($1103–3305)
Total (N = 738)	$2136 ($1554–2719)	$372 ($174–570)	$1326 ($979–1673)

Table 21. Coefficients associated with patient baseline characteristics for annual patient time and caregiver time costs and out-of-pocket costs in a Canadian HCV survey study.

Predictor	Annual patient and caregiver time cost				Annual out-of-pocket cost			
	Coefficient	SE	t	P-value	Coefficient	SE	t	P-value
(Constant)	5291.14	2329.15	2.27	0.02	1012.71	1217.99	0.83	0.41
Treatment	184.66	1281.15	0.14	0.89	1511.28	669.89	2.26	<0.05
Viral clearance	-893.79	916.62	-98	0.33	-626.31	479.33	-1.31	0.19
Cirrhosis	2758.79	950.32	2.9	0.004	369.4	496.95	0.74	0.46
HCC	1992.02	2234.15	0.89	0.37	1594.62	1168.31	1.36	0.17
Transplantation	10028.23	1449.33	6.92	<0.0001	1013.5	757.9	1.34	0.18
Age	-73.51	40.08	-1.83	0.07	17.58	20.96	0.84	0.4
Gender	394.75	708.36	0.56	0.58	-628.3	370.43	-1.7	0.09
Marital status	363.69	710.33	0.51	0.61	143.24	371.45	0.39	0.7
Education	-198.53	724.06	-0.27	0.78	54.6	378.64	0.14	0.89
Ln income	-188.38	90.88	-2.07	0.04	-121.61	47.53	-2.56	<0.05
ICED	281	325.44	0.86	0.39	1511.28	669.89	0.18	<0.05

ICED, Index of Co-Existent Disease; SE, standard error.

12. Figures.

Figure 1. Simplified Markov model structure for simulating prognosis of HCV in the current revision.

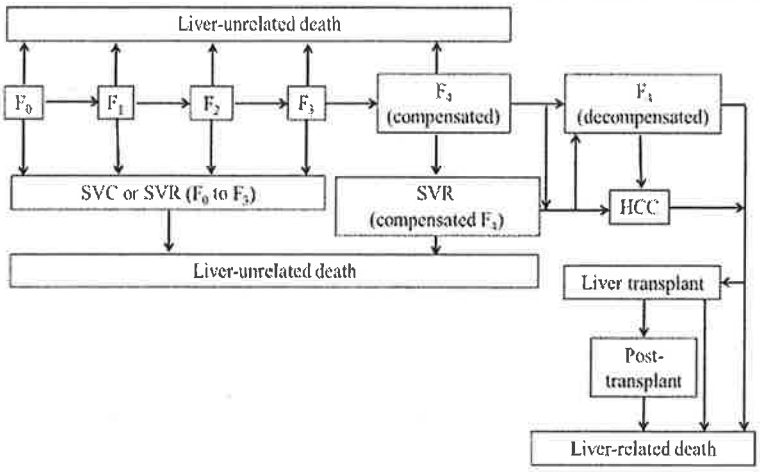


Figure 2. Subtree for health state "Fibrosis stage 0 with negative HCV RNA".

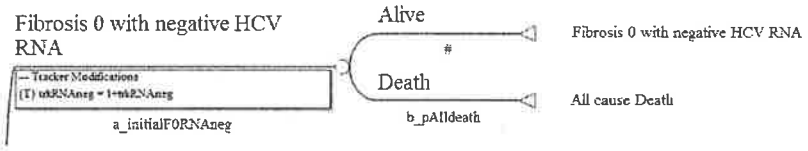


Figure 3. Subtree for health state "Fibrosis stage 0 with positive HCV RNA".

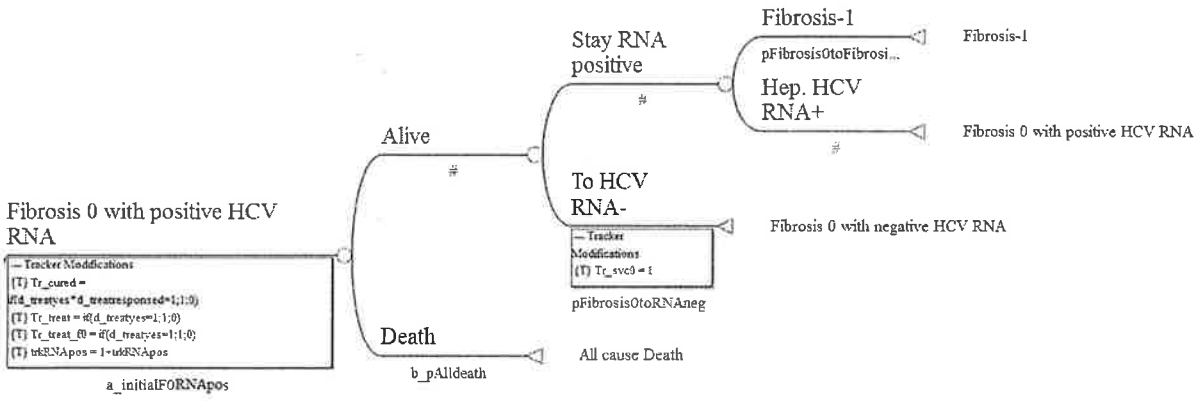


Figure 4. Subtree for health state "Fibrosis stage 1".

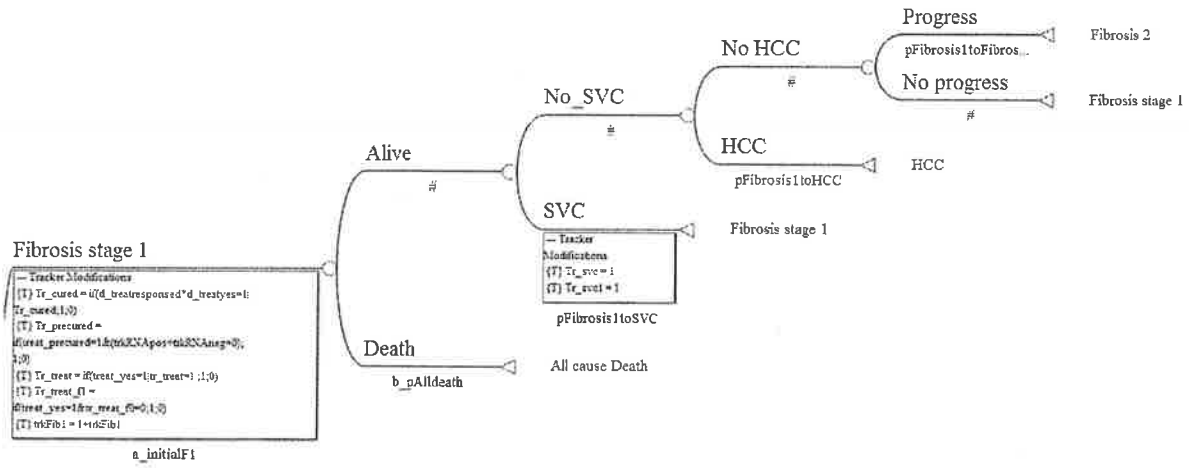


Figure 5. Subtree for health state "Fibrosis stage 2".

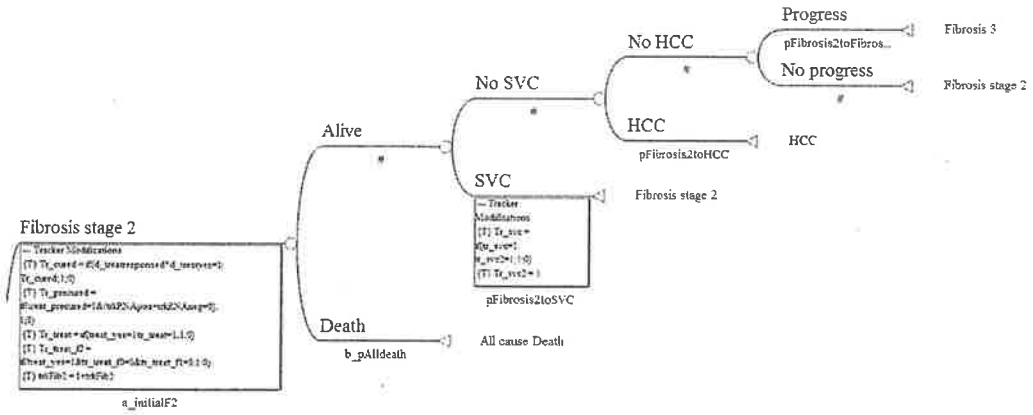


Figure 6. Subtree for health state "Fibrosis stage 3".

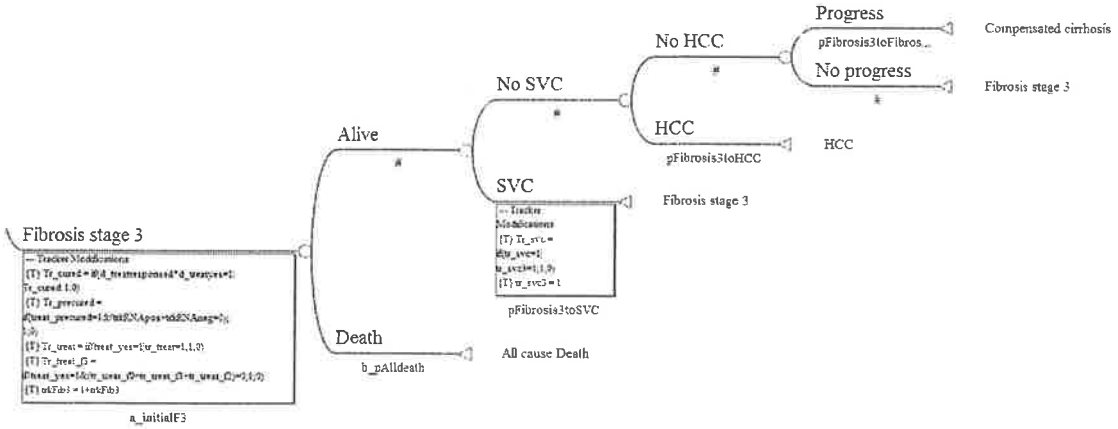


Figure 7. Subtree for health state "Compensated cirrhosis".

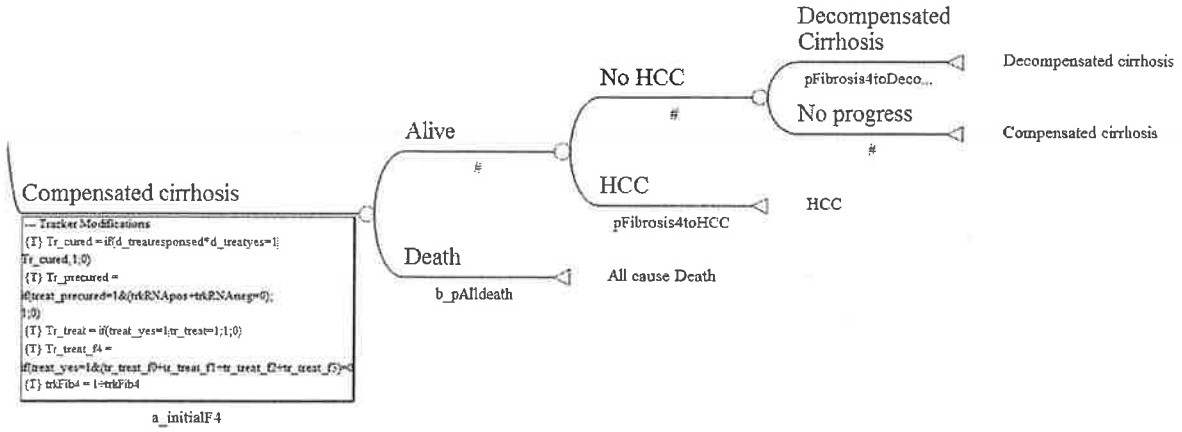


Figure 8. Subtree for health state "Decompensated cirrhosis".

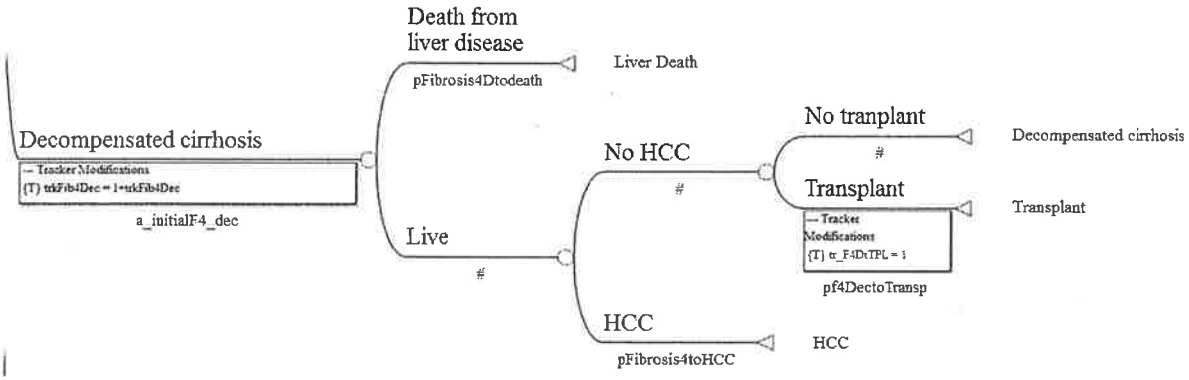


Figure 9. Subtree for health state "HCC".

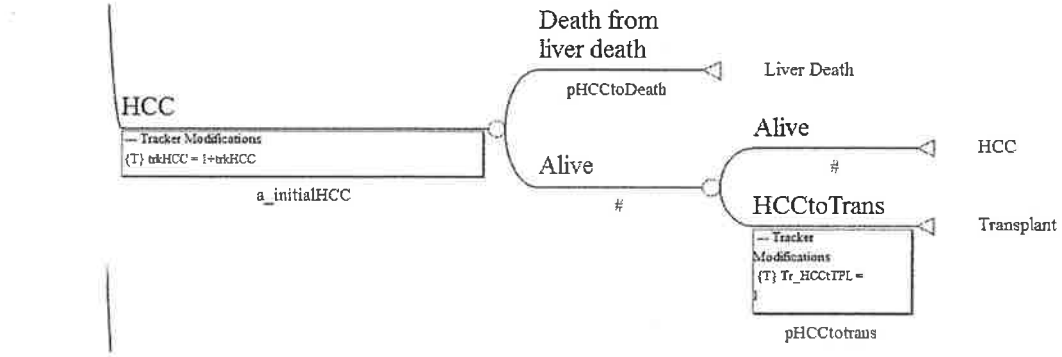
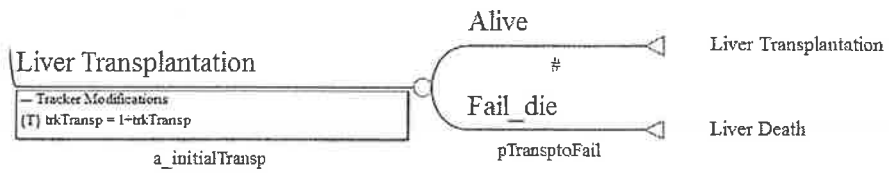


Figure 10. Subtree for health state "Liver transplantation".



Appendix 1. The study ethics approval letter for the fifth revision of HCV prognostic model for 1986-1990 HCV compensation claimants.

UNIVERSITY OF TORONTO

OFFICE OF THE VICE-PRESIDENT, RESEARCH AND INNOVATION

PROTOCOL REFERENCE # 29616

January 6, 2014

Dr. Murray Krahn
DEPT OF MEDICINE
FACULTY OF MEDICINE

Dear Dr. Krahn,

Re: Your research protocol entitled, "The fifth revision plan on estimating the prognosis of Canadians infected with the Hepatitis C virus through the blood supply, 1986-1990"

ETHICS APPROVAL	Original Approval Date: January 6, 2014 Expiry Date: January 5, 2015 Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

OFFICE OF RESEARCH ETHICS
McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1S8 Canada
Tel: +1 416 946-3273 • Fax: +1 416 946-5763 • ethics.review@utoronto.ca • http://www.research.utoronto.ca/for-researchers/ethics-human-research/

Appendix II. The survey package measuring clinical physicians' treatment preferences for survival compensation claimants with CHC.

I. INFORMED CONSENT FORM

I volunteer to participate in a research project conducted by Dr. Murray Krahn from the Toronto Health Economics and Technology Assessment (THETA) Collaborative at the University of Toronto.

I understand that this project is designed to gather information to predict long-term health outcomes in a cohort of patients who have acquired chronic hepatitis C (CHC) through blood transfusion or blood products from 1986 to 1990 in Canada and who are currently qualified to receive compensation for antiviral therapy for CHC-related complications from a trust fund set by the Canadian Federal, Provincial, and Territory governments.

I understand that this survey will assess physician's preferences regarding the use of new antiviral regimens in this CHC compensation cohort.

I understand that my participation in this survey is voluntary and that I may refuse to volunteer, decline to answer any questions and withdraw from the survey at any time without giving any reasons.

I understand that my participation in this survey is unlikely to cause any risks, harm or inconvenience to me or my patients.

I understand that the generated outcomes of this survey will be included in the study final report and might be published in a relevant medical journal.

I understand that my personal information and generated data will be strictly protected in a secured computer and locked in a safe box in the administrative office at THETA.

I understand that all information from this survey will be considered confidential and access to this data will be limited to the principal investigator, study coordinator and data analyst.

I understand that my personal information will be encrypted as codes in the survey and data analysis and the final report and manuscript will not include any identifiable information.

Certificate of consent:

I have read the foregoing information or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant: _____

Signature of Participant: _____

Date (DD/MM/YYYY): _____

Please fax back the signed consent form to 416-946-3719 with attention to Dr. Murray Krahn.

II. CHARACTERISTICS OF SURVEY PATICIPANT

1. **Please provide the following personal information:**

   Birth year: _____Gender: ☐ Male / ☐ Female

2. **Please outline your educational background**

   MD completed year: _____

   Master's degree completed year: _____

   PhD completed year: _____

3. **Please describe your university affiliations**

   Position: _____

   Faculty/Department: _____

   Institution: _____

4. **Please describe your clinical practice**

   Type of clinical setting:

   - ☐ Tertiary care hospital
   - ☐ Community medical center
   - ☐ Ambulatory care (physician's office) not attached to hospital
   - ☐ Other: (please specify) _____

   Clinical specialty:

   - ☐ Hepatology
   - ☐ Gastroenterology
   - ☐ Infectious diseases
   - ☐ Internal medicine
   - ☐ Other: (please specify) _____

   Duration of clinical practice in your current specialty (years): _____

5. **Please provide information regarding chronic hepatitis C patients**

   Monthly number of patient visits for chronic hepatitis C in 2013:_____

Monthly number of patients receiving antiviral therapy for chronic hepatitis C in 2013: _____

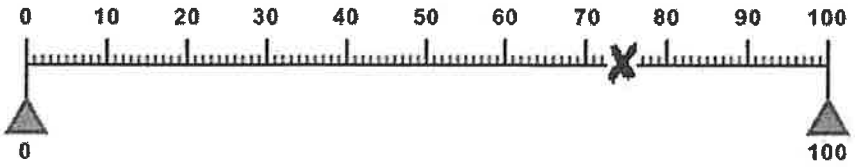
III. INSTRUCTIONS TO COMPLETE THIS SURVEY

This survey aims to understand how patients within the HCV compensation cohort are likely to be treated with antiviral therapy. In formulating your response, please consider how you are likely to treat HCV patients OVER THE NEXT TWO YEARS. We ask you to think ahead, because some of these regimens are not available in every jurisdiction at present. We will be considering the following treatment regimens:

a. Pegylated interferon plus ribavirin (PEG/RBV) (24 to 48 weeks)
b. PEG/RBV-based triple therapy with bocepreivr, telaprevir, or faldaprevir (24 to 48 weeks)
c. PEG-free therapy including the combination of ribavirin and three direct antiviral agents (12 weeks)
d. PEG/RBV-free therapy including sofosbuvir-based doublet with daclatasvir, ledipasvir or simeprevir (12 weeks)

Because HIV co-infection and previous failed antiviral treatment will affect treatment decisions, the CHC compensation cohort will be divided into four subgroups. You will read a brief description of baseline characteristics associated with the subgroup and the estimated clinical efficacy (sustained viral response (SVR)) and treatment discontinuation associated with antiviral regimens for the subgroup.

1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



2. If you decide to treat this subgroup, please indicate which regimen you are likely to use most frequently in this group: a

a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

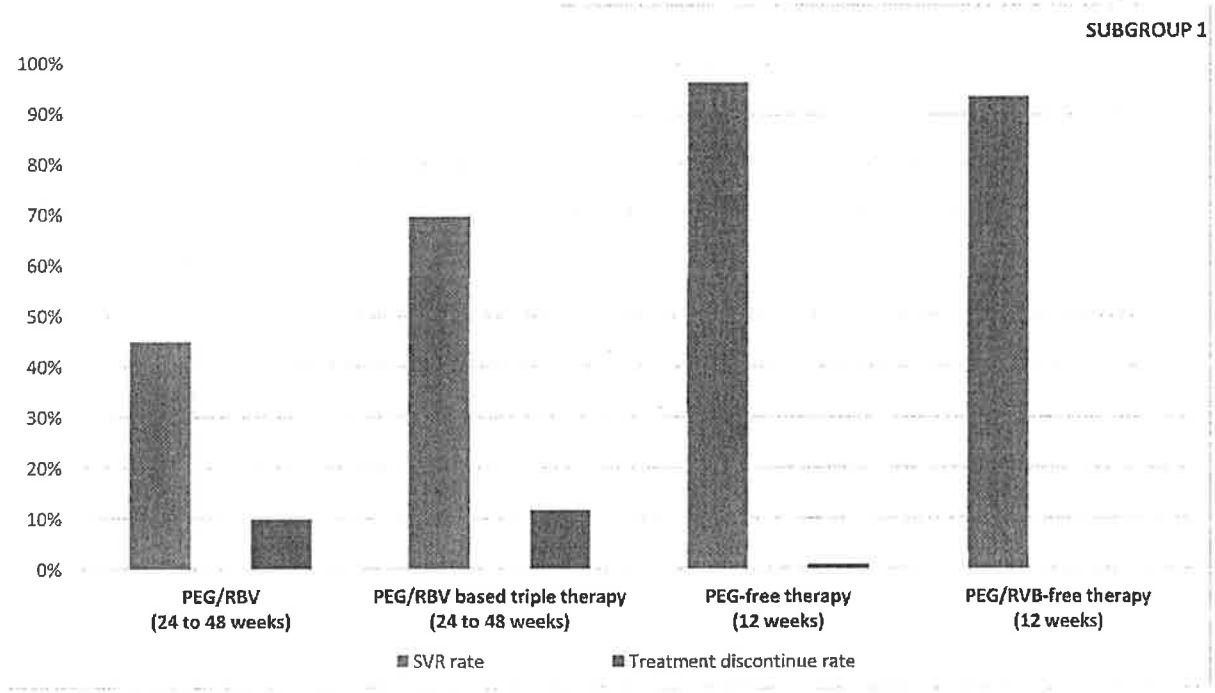
IV. QUESTIONNAIRES FOR THE FOUR PATIENT SUBGROUPS

Patient subgroup 1: Naïve patients without HIV co-infection

1. Baseline characteristics of patient subgroup 1

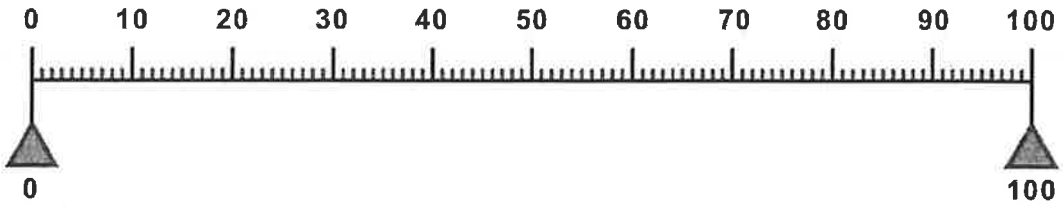
Baseline variable	%/mean ±SD
Age (years)	62.8 ± 20.2
Male gender	53.3%
Duration of HCV infection (years)	26.7 ± 4.8
Hemophilics	16.2%
Previous blood transfusion	81.9%
Distribution of fibrosis stage	
F0	63.5%
F1/F2	27.8%
F3	3.8%
F4	4.9%
Distribution of viral genotype	
1	74.4%
2 or 3	24.4%
4, 5 or 6	1.2%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 1 (naïve patients without HIV co-infection).



3. Survey questions for patient subgroup 1 (naïve patients ***without*** HIV co-infection).

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (naïve patients ***without*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (naïve patients ***without*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

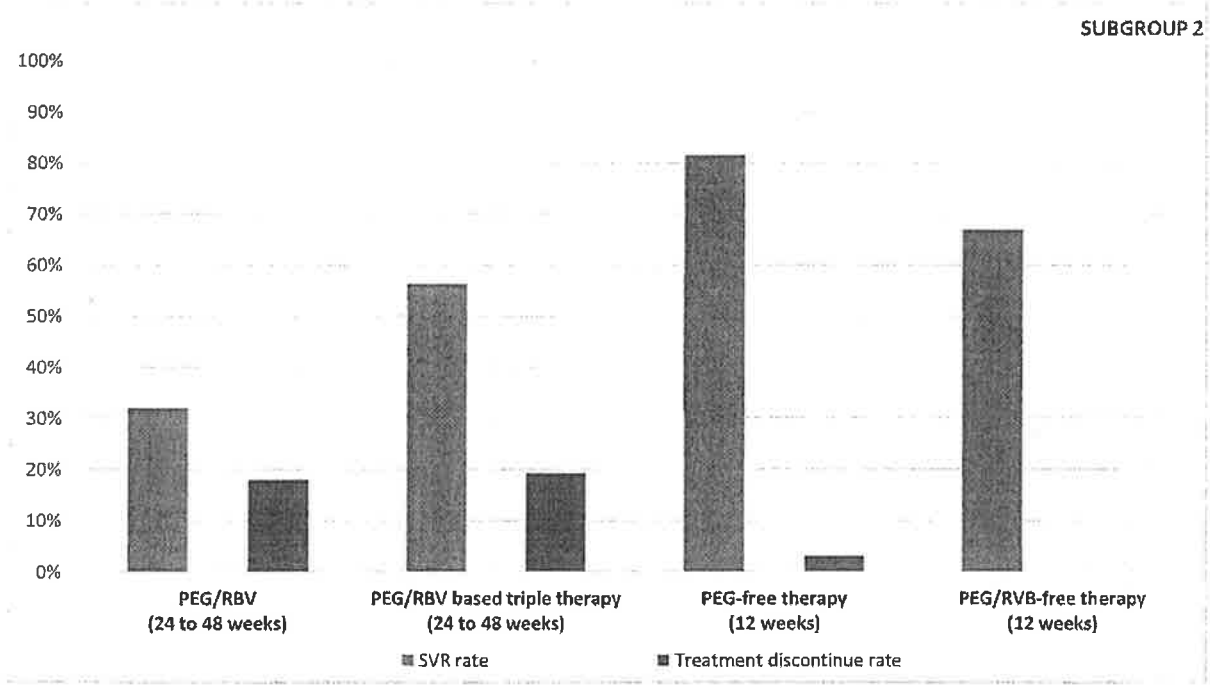
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 2: Naïve patients with HIV co-infection

1. Baseline characteristics of patient subgroup 2.

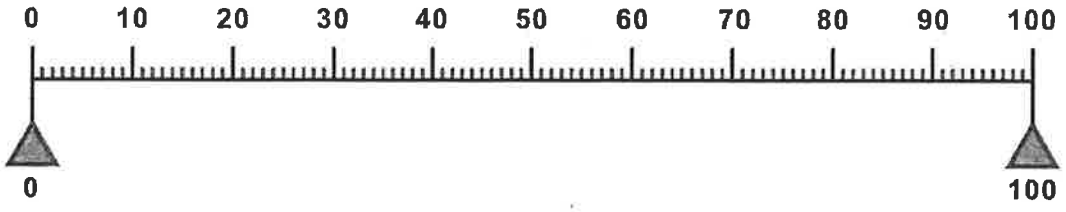
Baseline variable	%/mean ±SD
Age (years)	47.6 ± 11.2
Male gender	96.3%
Duration of HCV infection (years)	25.0 ± 1.0
Hemophilics	97.3%
Previous blood transfusion	2.8%
Distribution of fibrosis stage	
F0	39.4%
F1/F2	39.4%
F3	5.5%
F4	15.6%
Distribution of viral genotype	
1	75.0%
2 or 3	16.7%
4, 5 or 6	8.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 2.



3. Survey questions for patient subgroup 2 (naïve patients ***with*** HIV co-infection).

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (naïve patients ***with*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (naïve patients ***with*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

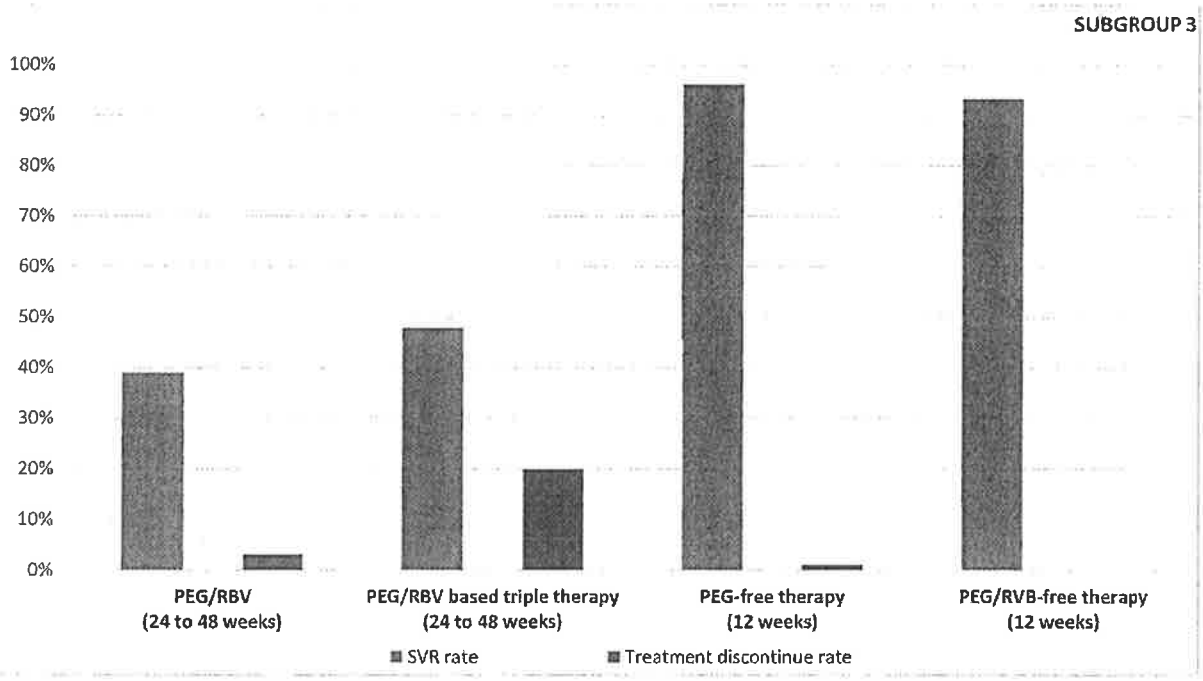
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 3: Previously treated patients without HIV co-infection

1. Baseline characteristics of patient subgroup 3.

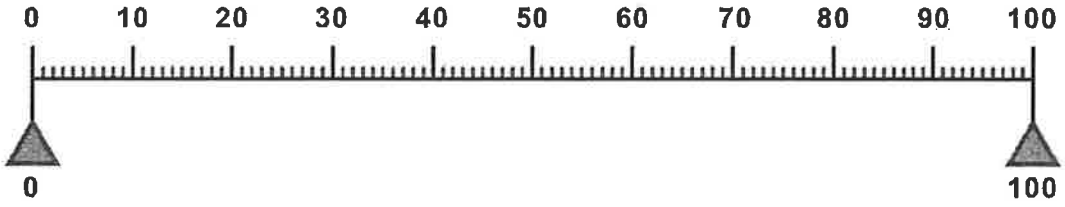
Baseline variable	%/mean ±SD
Age (years)	54.3 ± 14.0
Male gender	58.0%
Duration of HCV infection (years)	26.4 ± 5.2
Hemophilics	27.3%
Previous blood transfusion	71.4%
Distribution of fibrosis stage	
F0	0.0%
F1/F2	71.0%
F3	15.2%
F4	13.8%
Distribution of viral genotype	
1	74.4%
2 or 3	24.4%
4, 5 or 6	1.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 3.



3. Survey questions for patient subgroup 3 (previously treated patients ***without*** HIV co-infection)

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (previously treated patients ***without*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (previously patients ***without*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

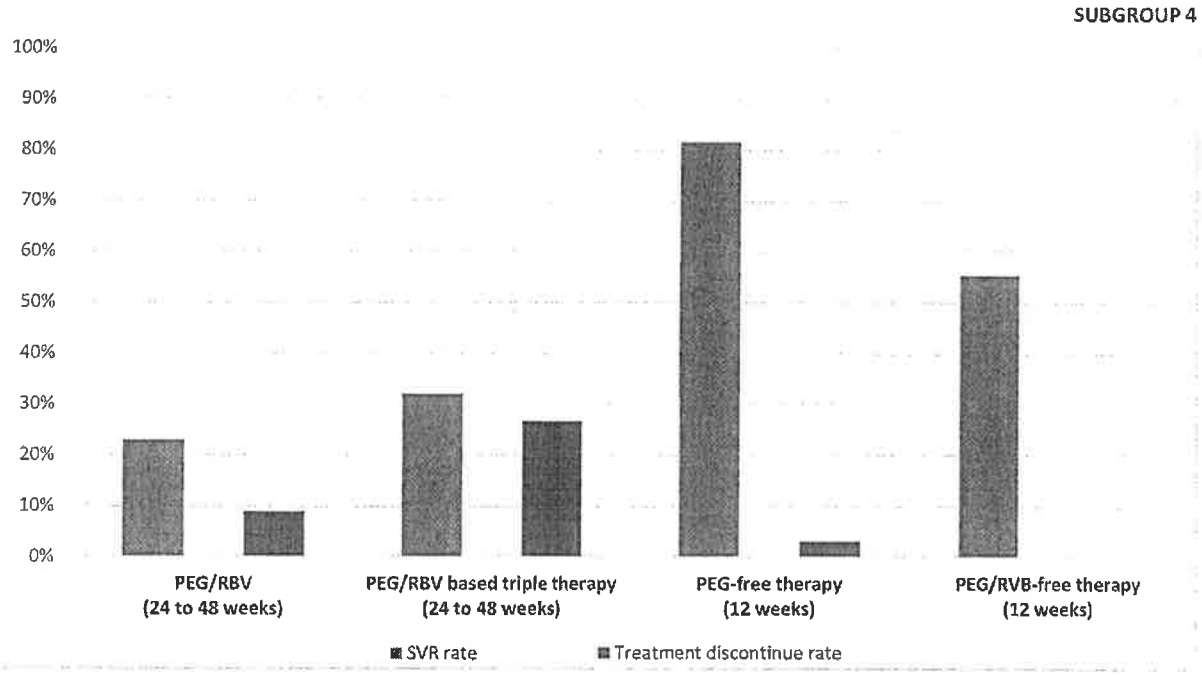
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 4: Previously treated patients with HIV co-infection

1. Baseline characteristics of patient subgroup 4.

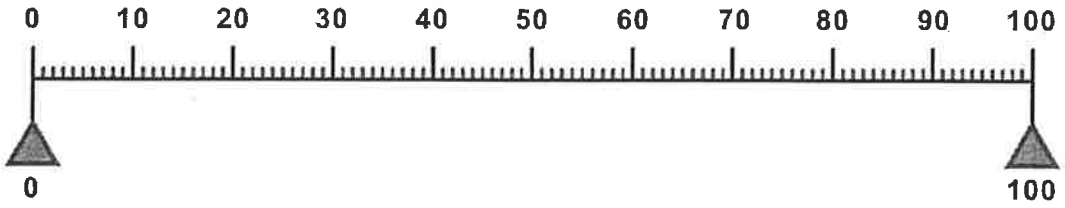
Baseline variable	%/mean ±SD
Age (years)	50.2 ± 8.2
Male gender	93.3%
Duration of HCV infection (years)	26.0 ± 1.7
Hemophilics	93.0%
Previous blood transfusion	7.0%
Distribution of fibrosis stage	
F0	0.0%
F1/F2	53.5%
F3	16.3%
F4	30.2%
Distribution of viral genotype	
1	75.0%
2 or 3	16.7%
4, 5 or 6	8.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 4.



3. Survey questions for patient subgroup 4 (previously treated patients ***with*** HIV co-infection)

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (previously treated patients ***with*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (previously patients ***with*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Many thanks for completing the survey questions for our study. You can fax back the signed information consent form and completed survey with attention to Dr. Murray Krahn.

Fax number is 416-946-3719.

This is Exhibit "B" referred to in the Affidavit of Murray Krahn sworn before me, this 16th day of March, 2015

A COMMISSIONER FOR TAKING AFFIDAVITS

CURRICULUM VITAE

Dr. Murray D. Krahn

A. DATE OF PREPARATION

January 2015

B. BIOGRAPHICAL INFORMATION

Business Address

Toronto Health Economics & Technology Assessment (THETA) Collaborative
144 College Street, Room 658
Toronto, ON M5S 3M2
Tel: 416-978-6608 Fax: 416-946-3719
E-mail: murray.krahn@theta.utoronto.ca

Degrees/ Education

1992-1993	Research Fellowship Clinical Decision Making, New England Medical Center, Tufts University
1990-1993	Fellowship, General Internal Medicine, University of Toronto
1991	M.Sc. Clinical Epidemiology, McMaster University
1986-1990	Post-graduate training, Internal Medicine, University of Toronto
1982	M.D. University of Manitoba
1978	B.A. Philosophy, University of Winnipeg

Employment

2007 – Present	Director, Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto; Professor, Department of Medicine, Division of General Internal Medicine and Clinical Epidemiology, University of Toronto; Professor, Faculty of Pharmacy, University of Toronto
2001 - 2007	Associate Professor, Department of Medicine, Division of General Internal Medicine and Clinical Epidemiology, University of Toronto
2006 – Present	Adjunct Scientist, Institute for Clinical Evaluative Sciences (ICES) Senior Scientist, Toronto General Research Institute
2005 – Present	F. Norman Hughes Chair in Pharmacoeconomics, Faculty of Pharmacy, University of Toronto
2000 – 2005	Associate Director, Clinical Epidemiology Program, Health Policy, Management and Evaluation, University of Toronto
1995	Scientist, Toronto General Research Institute General Internal Medicine, University Health Network

Honours and Awards

2014	The Dr. Jill M. Sanders Award of Excellence in Health Technology Assessment, CADTH
2009	Senior Researcher Award, Association of Faculties of Pharmacy of Canada
2007	David Sackett Senior Investigator Award, Canadian Society for Internal Medicines
2005	Inaugural holder of the F. Norman Hughes Chair in Pharmacoeconomics, Faculty of Pharmacy

2005	Eugenie Stuart Award for Excellence in Course/Program Development & Coordination, Department of Health Policy, Management, and Evaluation, University of Toronto
2001 – 2007	Investigator Award, Canadian Institutes for Health Research
2004	Wightman Berris Academy Teaching Individual Teaching Award in the Category of "Health Professional Programs"
1996-1998	Arthur Bond Fellowship for Innovative Health Systems Research, Physicians' Services Incorporated Foundation
1992, 1995	Young Investigator of the Year, Society for Medical Decision Making
1990	Henry Christian Memorial Award, American Federation for Clinical Research, Outstanding abstract in Clinical Epidemiology
1990	Residents and Fellows Research awards, Clinical Epidemiology Category, Toronto General Hospital, University Health Network

Professional Affiliations and Activities

2015	Member, JDMI Research Steering Committee
2013	President, Society for Medical Decision Making; Co-Chair, Government Economic Advisory Board Advisory Board Organizing Committee; Chair, Decision Determinants Sub-Committee, Ontario Health Technology Advisory Committee (OHTAC) Co-Chair, Vaccine Pharmacoeconomics Workshop
2012	Public Engagement Sub-Committee, Health Quality Ontario Steering Committee, BRIDGES Governance Comittee
2010	Co-chair, Society for Medical Decision Making annual meeting Member, Ontario Health Technology Advisory Committee Co-chair, Health Technology Assessment Group, Applied Research Center in Cancer Control Mentor, Health Care, Technology, and Place, CIHR STIHR program, University of Toronto
2000 - 2010	Member, Advisory Committee to the Bone and Joint Decade Task Force on Neck Pain and its Associated Disorders
2005	Member, Drug Quality and Therapeutics Committee, Cancer Care Ontario Subcommittee, Ontario Ministry of Health and Long-term Care Chair, Clinical Strategies, Society for Medical Decision Making Annual Meeting, San Francisco
2004-2006	Chair, Membership Committee, Society for Medical Decision Making
2004	Chair, Health Economics Abstract Sessions, Society for Medical Decision Making Annual Meeting, Atlanta Board Member, CIHR/NCIC Canadian Prostate Cancer Research Initiative Editorial Board, Medical Decision Making
2002-2005	Trustee, Board of Directors, Society for Medical Decision Making
2001-2005	Associate Director, Clinical Epidemiology and Health Care Research Programme, Department of Health Administration, University of Toronto
2001-2004	Clinician Scientist Committee, Canadian Institutes for Health Research
2002	Bone and Joint Decade 2000 Task Force on Neck Pain and Associated Disorders
2000	Data Safety and Monitoring Committee; CLIP (Cancer of the liver, Italian Program) trial of alternate screening intervals for hepatocellular carcinoma Clinical Research Programme in Prostate Cancer, University Health Network Faculty Advisory Board, University of Toronto Medical Journal
1998-2010	Chair, working group commissioned by the Federal, Provincial and Territorial Governments of Canada, the Hepatitis C plaintiffs (1986-1999) and the Canadian Association for the Study of the Liver (CASL) to produce a model of the natural history of hepatitis C.
1998 – 2001	Member, Decision Analysis Group, UCLA-Rand Evidence Based Practice Center
1996 - 2000	Member, Scientific Advisory Panel, Canadian Coordinating Office of Health Technology Assessment (CCOHTA)

1996-1998	Member, Executive, Socio-behavioral Cancer Research Network, National Cancer Institute of Canada
1996	Co-chair, Short Courses, Society for Medical Decision Making Annual Meeting
1995-1996	Member, Ontario Ministry of Health Hepatitis B Control Program Committee
1994-1997	Editorial Board, Medical Decision Making
1993-1995	Member, Ontario Ministry of Health Guidelines Panel for Prostate Specific Antigen Utilization

Reviewer:

Dutch HTA Agency (Zorginstituut Nederland)
Canadian Institutes for Health Research
Annals of Internal Medicine,
Journal of the American Medical Association,
Medical Decision Making,
PharmacoEconomics,
ACP Journal Club,
Evidence Based Medicine,
Abstracts of Clinical Care Guidelines,
Pediatrics,
Alberta Heritage Foundation for Medical Research
Michael Smith Foundation
B.C. Lung Association,
Canadian Medical Association Journal
American Journal of Medicine
Quality of Life Research
Value in Health
Canadian Journal of Public Health
Canadian Journal of Respirology
Gastroenterology
Journal of the American Medical Association

Consultant:

Ontario Ministry of Health, Drug Quality and Therapeutics Committee,
New Drug Funding Program, Cancer Care Ontario

University Committees

January 2008	Member, Departmental Promotions Committee, Department of Medicine, University of Toronto
November 2007	Member, Planning Committee for the first GIM Faculty Day, Department of Medicine, University of Toronto
2005	HPME Ontario Research Chairs Search Committee Curriculum Committee, Accreditation Committee, Faculty of Pharmacy
2000-2005	Chair, PhD Admissions Committee, Clinical Epidemiology Program, University of Toronto PhD Committee, Communications Task Force, Curriculum Committees, Department of Health Policy, Management, and Evaluation
1999	Executive Committee, Clinical Epidemiology Program, University of Toronto
1997-2005	M.Sc. Admissions Committee, Clinical Epidemiology Program, University of Toronto
1995-1997	Urban Health Initiatives Committee, University of Toronto

Hospital Committees

1996-1998	Member, Executive, Socio-behavioral Cancer Research Network, National Cancer Institute of Canada
1996	Co-chair, Short Courses, Society for Medical Decision Making Annual Meeting
1995-1996	Member, Ontario Ministry of Health Hepatitis B Control Program Committee
1994-1997	Editorial Board, Medical Decision Making
1993-1995	Member, Ontario Ministry of Health Guidelines Panel for Prostate Specific Antigen Utilization

Reviewer:

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Journal of the American Medical Association,
Medical Decision Making,
PharmacoEconomics,
ACP Journal Club,
Evidence Based Medicine,
Abstracts of Clinical Care Guidelines,
Pediatrics,
Alberta Heritage Foundation for Medical Research
Michael Smith Foundation
B.C. Lung Association,
Canadian Medical Association Journal
American Journal of Medicine
Quality of Life Research
Value in Health
Canadian Journal of Public Health
Canadian Journal of Respirology
Gastroenterology
Journal of the American Medical Association

Consultant:

Ontario Ministry of Health, Drug Quality and Therapeutics Committee,
New Drug Funding Program, Cancer Care Ontario

University Committees

January 2008	Member, Departmental Promotions Committee, Department of Medicine, University of Toronto
November 2007	Member, Planning Committee for the first GIM Faculty Day, Department of Medicine, University of Toronto
2005	HPME Ontario Research Chairs Search Committee Curriculum Committee, Accreditation Committee, Faculty of Pharmacy
2000-2005	Chair, PhD Admissions Committee, Clinical Epidemiology Program, University of Toronto PhD Committee, Communications Task Force, Curriculum Committees, Department of Health Policy, Management, and Evaluation
1999	Executive Committee, Clinical Epidemiology Program, University of Toronto
1997-2005	M.Sc. Admissions Committee, Clinical Epidemiology Program, University of Toronto
1995-1997	Urban Health Initiatives Committee, University of Toronto

Hospital Committees

1999	Research Director, Division of General Internal Medicine, University Health Network
2005	Postgraduate fellowship committee

C. ACADEMIC HISTORY

Research Interests

My central area of research interest has been the application of decision analysis and economic evaluation to broad questions of health and clinical policy. This methodologic focus has been expressed in a variety of content areas including prostate cancer and viral hepatitis. More recent interests include evaluating the role of disease specific utility assessment, using administrative data to build longitudinal cost models, and evaluating the role of health technology assessment in pharmaceutical reimbursement decisions.

Research Awards (Applied)

1. The Canadian F.I.G.H.T. (Fluorenscence Image-Guided Help in Treating) Breast Cancer Surgical Trial
   Canadian Institutes of Health Research: Transitional Operating Grant

Principal Investigator:	Dacosta R
Co-Investigators	Done S, Easson A, Helyer L, Holloway C, Krahn M, Leong W, McCready D, Meiers P, Mew D, Panzarella T, Rosen C, Simpson J
2015 - 2020	$1,580,000
Major goals of the project:	See title
% of overlap with current application	0%

2. Improving Triage and Infroming Capacity Needs for Patients with Severe Aortic Stenosis undergoing Transcatheter Aortic Valve Implantation (TAVI): A Pan-Canadian Evaluation
   Canadian Instititues of Health Research

Principal Investigator:	Wijeysundera H
Co-Investigators:	Asgar A, Austin P, Bainey K, Berta W, Gagliardi A, Hoch J, Knudtson M, Ko D, Kuluski K, Lauck S, Miller F, Nadeem S, Pelletier M, Piazza N, Potter B, Rodes Cabau J, Tu J, Webb J, Wong W, Wood D
Collaborators:	Booker J, Cohen E, Daneault B, Denereux P, Kass M, Krahn M, Peterson m, Welsh R, Zimmermann R
2015 - 2019	1,462,931
Major goals of the project:	See title
% of overlap with current application	0%

3. The impact of periodontitis on the time to progression to insulin therapy among Canadian First Nations and Inuit with type 2 diabetes managed by oral anti-diabetic medications
   Canadian Diabetes Association 2014 operating grant competition

Principal Investigator:	Azarpazhooh A
Co-Investigators:	Banerji A, **Krahn M,** Lebovic G, Mamdani M, Shah P, Stewart S, Tenenbaum H
2014 – 2016	$152,329
Major goals of the project:	See title
% of overlap with current application	0%

4. Evaluation of Telehomecare for Patients with Congestive Heart Failure or Chronic Obstructive Pulmonary Disease
TVN - Strategic Impact Grant

Principal Investigator:	**Krahn M** and Rac V
Co-Investigators:	Alter D, Schull M, Abrahamyan L, Pechlivanoglou P, Wong W, Shahid N, Sahakyan Y, Fan I
2015 - 2017	$518,972
Major goals of the project:	See title
% of overlap with current application	0%

5. Pan-Canadian Evvironmental Scan of End-of-Life Care Policies and Practices in breast cancer
Breast Cancer Foundation

Principal Investigator:	**Krahn M**
Co-Investigator:	Rac V, Wong W, Pechlivanoglou P, Miller F, Abrahamyan L
2015-2018	$434,882
Major goals of the project:	See title
% of overlap with current application	0%

Research Awards (Granted)
Peer Review

1. Vivia Hemodialysis System
MaRS EXCITE: Baxter Healthcare Corporation

Principal Investigator(s)	**Krahn M**, Rac V
Co-Investigators:	Abrahamyan L, Mitsakakis N
2014-2017	$1, 813,000.12
Major goals of the project:	See title
% of overlap with current application	0%

2. The impact of periodontitis on the time to progression to insulin therapy amony Canadian First Nations and Inuit with type 2 diabetes managed by oral anti-diabetic medications.
Canadian Diabetes Association

Principal Investigator:	Azarpazhooh A
Co-Investigators	**Krahn M**, Banerji A, Lebovic G, Mamdani M, Prakeshkumar S, Stewart S, Tennenbaum H
2014-2016	$152,329
Major goals of the project:	See title
% of overlap with current application	0%

3. Service Models and Cost-effectiveness of Preoperative Care in Ontario
Health Quality Ontario (HQO)

Principal Investigator: Rac V
Co-PI: **Krahn M**
Co-Investigators: Abrahamyan L, Pechlivanoglou P, Mitsakakis N, Carcone S
2014 - 2017 $471,799
Major goals of the project: See title

% of overlap with current application 0%
Grant No. 497336

4. Request for proposal for Evaluation Services - Value Demonstrating Initiative on COPD: Evaluation of Value Demonstrating Initiative on COPD
The Lung Association
Principal Investigator: **Krahn M**
Co-Investigators: Rac V, Abrahamyan L, Pechlivanoglou P, Mitsakakis N
2014-2017 $397,434
Major goals of the project: See title
% of overlap with current application 0%
Grant No. not yet set up

5. Toronto Health Economics and Technology Assessment Collaborative (THETA)
Health Quality Ontario (HQO)
Principal Investigator: **Krahn M**
Co-investigators: Rac V, Pham B, Miller F, Abrahamyan L, Pechlivanoglou P, Carcone S, Bielecki J, Lim M
4/2014 – 3/2017 $4,800,000
Major goals of the project: See title
% of overlap with current application 0%
Grant No. 496569

6. Pathways to Procurement: Processes, Rationales & Options for Investing in Health Technology Innovation
Canadian Institute of Health Research (CIHR)
Principal Investigator: Miller F
Co-Investigators: Lehoux P, **Krahn M**, Peacock S, Rac V, Pham B
2014-2018 $354,718

Major goals of the project: See Title
% of overlap with current application: 0%
Grant No. MOP 133514

7. Using Administrative Health Care Data to Inform Cancer Care Policy in Canada
Canadian Institute of Health Research (CIHR)
Principal Investigator: **Krahn M**
Nominated PI: de Oliveira C
Co-Investigators: Matheson G, Coldman A, Cooper D, Joyce M, Rousseau J, Dragomir E, Earle C, Hoch J, Mittman N, Peacock S, Skedgel C, Turner D

2014-2017	$398,814 (CIHR) $75,000 (MOHLTC - partner)
Major goals of the project:	See Title
% of overlap with current application:	0%

8. Ecologically Optimizing Exercise Maintenance in Men and Women Pos-Cardiac Rehabilitation: A Randomized Controlled Trial of Efficacy with Economics (ECO-PCR)
Heart and Stroke Foundation of Canada

Principal Investigator(s)	Reid R and Grace S
Co-Investigators:	Blanchard C, Chessex C, Harris J, Kingsbury K, Manuel D, Mark A, Mullen K, Pipe A, **Krahn M**
2014 - 2017	$274,825
Major goals of the project	See title
% of overlap with current application	0%

9. Development of a Utility Weighting Function for the Bladder Utility Symptom Scale (BUSS-U)
Canadian Cancer Society Research Institute (CCSRI)

Principal Investigator:	**Krahn M**
Co-Investigators:	Kulkarni G, Alibhai S, Chin J, Chung P, Finelli A, Perlis N, Sridhar S, Tomlinson G, Boehme K, Bremner K
2/2014 – 1/2017	$299,900
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 702607

10. Cross sectional and longitudinal measures of quality of life and utility among patients with chronic hepaitis C virus infection
Canadian Institutes of Health Research (CIHR)

Principal Investigator	**Krahn M**
Nominated PI:	Wong W
Co-Investigators:	Krahn M, Bruneau J, Feld J, Feng Z, Lee SS, Mitsakakis N, Myers R, Pechlivanoglous P, Powis J, Rac V
2014 - 2015	$100,000

11. Estimating the Cost of Non-dialysis Health Care Among Dialysis Patients
Ontario Renal Network/Cancer Care Ontario

Principal Investigator:	**Krahn M**
Co-Investigators:	Rac V, de Oliveira C, Mendelssohn D, McFarlane P, Bremner K
11/2013 – 7/2015	$189,952
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 495837

12. Evaluation of Telehomecare for Patients with Congestive Heart Failure or Chronic Obstructive Pulmonary Disease

Ministry of Health and Long-Term Care / BRIDGES

Principal Investigator:	**Krahn M**
Co-Principal Investigators:	Abrahamyan L, Pechlivanoglou P, Mitsakakis N
11/2013 – 12/2017	$436,828
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 470530

13. Clinical and Cost-effectiveness of MedsCheck in Ontario Seniors: A Mixed Methods Study

Canadian Pharmacists Association

Principal Investigator:	**Krahn M**
Co-Investigators:	Rac V, Pechlivanoglou P, Grootendorst P, Mitsakakis N, Bowen J, Abrahamyan L, Priest S, Mahdi M
9/2013 – 03/2016	$236,626.80
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 495679

14. The mapping of the MFSAF and MPNSAF to the EQ-5D in a representative population of patients living with Myelofibrosis

Sanofi-Aventis Canada Inc.

Principal Investigator:	**Krahn M**
Co-Investigators:	Mitsakakis N, Bremner K
12/2013 - 12/2014	$80,000
Major goals of the Project:	See title
% of overlap with current application	0%

Grant No. 144414

15. Canadian Institutes of Health Research (CIHR) - Transformation of Indigenous Primary Healthcare Delivery (FORGE AHEAD): Community-driven Innovations and Strategic Scale-up Toolkits

Principal Investigator:	Harris S.
Co-Investigators:	Baxter E, Houle L, Jacobs S, Kandukur K,; Littlechild RW, McComb IK, McDonald HL, Montour D, Morach JE, Nose MA, O'Keefe T, Redmond D, Spade D, Tischer C, Zeiller SD; Barre DE, Bhattacharyya O, Dannenbaum D, Dawson KG, Dyck RF, Episkenew JM, Green ME, Hanley AJ, Lavallee B, Macaulay AC; McComber AM; Parry MJ; Reichert SM; Salsberg JS; Thind A, Tobe SW, Toth EL, Walsh AM; Wortman J, Zwarenstein MF
Collaborators:	**Krahn M**, de Oliveira C
2013 – 2018	$500,000 / year ($2,500, 000)
Major goals of the project:	See title
% of overlap with	0%

16. Center for the Evaluation of Technological Innovation (CETI)

Canada Foundation for Innovation (CFI)

Principal Investigator:	**Krahn M**
Co-Investigators:	Miller F, Cadarette S, Wijeysundera H, Hoch J, Grootendorst P, Ungar W, Lemieux-Charles L, Coyte P.
2013-2018	$2,999,834
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. NIF 2012 #31001	

17. Home Sleep Study with ApneaDX for the diagnosis of obstructive sleep apnea: a pragmatic randomized controlled trial
MaRS Excellence in Clinical Innovation and Technology Evaluation (EXCITE)
Health Quality Ontario (HQO)

Principal Investigator:	**Krahn M**
Co-Principal Investigator:	Fitzpatrick M
Co-Investigators:	Rac V, Pham B, Pechlivanoglou P, Abrahamyan L.
4/2013 – 8/2014	$414,991 (EXCITE)
2014 - 2015	$339,318 (HQO)
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. 495183	

18. Toronto Health Economics and Technology Assessment Collaborative (THETA)
Health Quality Ontario (HQO)

Principal Investigator:	**Krahn M**
Co-investigators:	Alibhai S, Bayoumi A, Bauch C, Chaim B, Beyene J, Bremner K, Carcone S, Detsky A, Fowler R, Englesakis M, John-Baptiste A, Einarson T, Hoch J, Chen M, Laporte A, Mittman N, MacKeigan L, Naglie G, Naimark D, Pham B, Sander B, Thein HH, Tomlinson G, Ungar W, Urbach D.
4/2013 – 3/2014	$1,768,656
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. 494551	

19. Study of Tumour RNA Disruption Assay (RDA) as a predictive tool for response to Neoadjuvant Chemotherapy in Breast Cancer – A prospective Mixed-Methods Study
MaRS Excellence in Clinical Innovation and Technology Evaluation (EXCITE)

Principal Investigator:	**Krahn M**
Co-Investigators:	Rac V, Pechlivanoglou P, Pham B, Abrahamyan L, Carcone S, Wong J, Mitsakakis N
6/2013 – 6/2015	$1,160,423.60
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 495462

20. An RCT and economic analysis of three exercise delivery methods in men with prostate cancer on ADT
Canadian Institutes of Health Research (CIHR)

Principal Investigator:	Shabbir A
Co-Investigators:	Culos-Reed, S, **Krahn M**, Lukka H, Matthew A, Ritvo P, Sabiston C, Santa Mina D, Segal R, Tomlinson, G, Warde P
10/2013 – 9/2018	$781,091
Major goals of the project:	See title
% of overlap with current application	0%

21. A Phase II RCT and economic analysis of three exercise delivery methods in men with prostate cancer on ADT
Prostate Cancer Canada

Principal Investigator:	Shabbir A
Co-Investigators:	Culos-Reed, S, **Krahn M**, Matthew A, Ritvo P, Sabiston C, Santa Mina D, Segal R, Tomlinson, G, Warde P
7/2013 – 6/2015	$195,796
Major goals of the project:	See title
% of overlap with current application	0%

22. Phase-Specific and Lifetime Medical Costs of Care for Childhood Cancer in British Columbia and Ontario
Canadian Institutes of Health Research (CIHR)

Principal Investigator:	McBride M
Co-PI:	**Krahn M**
Co-Investigators:	de Oliveira C, Greenberg M, Nathan P, Peacock S, Rogers P
2012 – 2015	$377,886
Major goals of the project:	See title
% of overlap with current application	0%

Grant No. 20200

23. Developing and validating the Bladder Utility Symptom Scale (BUSS) - A disease specific utility Instrument For bladder cancer health related quality of life
Canadian Institutes of Health Research

Principal Investigator:	**Krahn M**, Kulkarni G
Co-Investigators:	Finelli A, Alibhai S, Perlis N, Ritvo P
10/2012-9/2015	$278,960
Major goals of the project:	See title
% of overlap with current application	0%

24. Stroke units in Ontario: characteristics and costs associated with effectiveness
Ontario Stroke Network

Principal Investigator:	**Krahn M**
Co-Investigators:	Kapral M, Ieraci L, Rac V,
9/2012-3/2014 :	$100,000
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. OSN 1207-000150	

25. Toronto Health Economics and Technology Assessment Collaborative (THETA)
Health Quality Ontario (HQO)

Principal Investigator:	**Krahn M**
Co-investigators:	Alibhai S, Bayoumi A, Bauch C, Chaim B, Beyene J, Bremner K, Carcone S, Detsky A, Fowler R, Englesakis M, John-Baptiste A, Einarson T, Hoch J, Chen M, Laporte A, Mittman N, MacKeigan L, Naglie G, Naimark D, Pham B, Sander B, Thein HH, Tomlinson G, Ungar W, Urbach D.
2012 - 2013	$1,768,656
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. 492530	

26. A Population-based outcome and economic evaluation of interventions for gastric cancer
Canadian Institutes of Health Research (CIHR)

Principal Investigator:	Coburn N
Co-Investigators:	Johnson A, **Krahn M**, Paszat L, Earle C, Law C, Karanicolas P, Kiss A, Wright F, Dobrow M, Irish J, McLeod R, Mahar A, Brar S, Dixon M
2012 – 2014	$245,200
Major goals of the project:	See title
% of overlap with current application	0%

27. Investigating the process of how expert-consult teams deliver home-based palliative care in two provinces

Canadian Institute of Health Research (CIHR)

Principal Investigator:	Seow H
Co-Investigators:	Austin P, Barbera L, Brazil K, Fainsinger R, Fassbender K, **Krahn M**, Marshall D, Pereira J, Sussman J
10/2011 – 09/2014	$387,917
Major goals of the project:	See title
% of overlap with current application	0%

28. A pharmacoeconomic policy model for hepatitis C: development and applications
Canadian Institute of Health Research (CIHR)

Principal Investigator:	Thein HH
Co-Investigators:	Dore G, Earle C, Feld J, Fisman D, **Krahn M**, Wong WW

10/2011 – 09/2013 $133,475
Major goals of the project: See title
% of overlap with current application 0%

29. Impact of Patterns of Current Care on the Burden of Chronic Hepatitis C In British Columbia, Canada
Canadian Liver Foundation
Principal Investigator: **Krahn M**
Co-Investigators: Chen WD
2011 – 2012 $355,300
Major goals of the project: See title
% of overlap with current application 0%
Grant No. CLF-Krahn Liver Research Trust Fund

30. Specialized Multidisciplinary Community-Based Care for Chronic Wounds Study
Ministry of Health and Long-Term Care (MoHLTC)
Principal Investigator: **Krahn M**
2011 – 2013 $300,100
Major goals of the project: See title
% of overlap with 0%
Grant No. 06403D

31. Heart Failure (Multi-Disciplinary Community Care) Clinics Field Evaluation Research Project
Ministry of Health and Long-Term Care (MoHLTC)
Principal Investigator: **Krahn M**
2010 – 2012 $240,449
Major goals of the project: See title
% of overlap with 0%
Grant No. 06403B

32. Pressure Ulcers Multi-disciplinary Team via Telemedicine (PUMTT)
Ministry of Health and Long-Term Care (MoHLTC)
Principal Investigator: **Krahn M**, Stern A
Co-investigators: Baker R, Levine L, Jeffs L, Harris C, Alibhai S, Woodbury G, Zwarenstein M, Teague L
2010 – 2012 $299,109
Major goals of the project: See title
% of overlap with current application 0%
Grant No. 06403C

33. Pressure Ulcers Multi-disciplinary Team via Telemedicine (PUMTT)
Canadian Patient Safety Institute
Principal Investigator: **Krahn M**, Stern A
Co-Investigators: Baker R, Levine L, Jeffs L, Harris C, Alibhai S, Woodbury G, Zwarenstein M, Teague L
2010 – 2012 $247,683

Major goals of the project: See title
% of overlap with current application 0%
Grant No. RFA09-1200-ON

34. Pressure Ulcers Multi-disciplinary Team via Telemedicine (PUMTT)
Community Care Access Centre
Principal Investigator: **Krahn M**, Stern A
Co-Investigators: Baker R, Levine L, Jeffs L, Harris C, Alibhai S, Woodbury G, Zwarenstein M, Teague L
2010 – 2012 $45,000
Major goals of the project: See title
% of overlap with current application 0%

35. The Economic Burden of Patient Safety
Canadian Patient Safety Institute (CPSI)
Principal Investigator: Etchells E
Co-Investigators: Baker M, Shojania K, **Krahn M**, McDonald A, Taggar R, Matlow A, Daneman N
2010 – 2012 $448,550
Major goals of the project: See title
% of overlap with current application 0%

36. Modeling and economic evaluation of hepatitis C epidemic mitigation strategies in Australia
National Health and Medical Research Council (NHMRC) Project Grant
Principal Investigator: Wilson DP, Thein HH, **Krahn M**
Co-Investigators: Dore G, Maher L, Kaldor J
2010 – 2012 $448,550
Major goals of the project: See title
% of overlap with current application 0%

37. Evaluation of a model for assessment and treatment of hepatitis C virus among injecting drug users in the opiate pharmacotherapy setting
NHMRC Partnership Projects
Principal Investigator: Dore G, Haber P, Grebely J, Day C, Treloar C, Ryan L, Thein HH
Co-Investigators: Jauncey M, **Krahn M**, Batey R, Loveday S, Bath N
2010 – 2014 $1,495,188
Major goals of the project: See title
% of overlap with current application 0%

38. Assessing the Impact of Policy Interventions for Problematic Prescription Opioid Use and Related Harms at a Popuulation Level
Canadian Institute of Health Research (CIHR)

Principal Investigator:	Arratoon C, Fischer B, Kendall P, Lynch M, Rehm J
Co-I:	Goldner E, **Krahn M**
2010 – 2011	$200,000
Major goals of the project:	See title
% of overlap with current application	0%

39. Assessing Interventions for Protecting Vulnerable Population during the 2009 H1N1 Pandemic
Canadian Institute of Health Research (CIHR)

Principal Investigator:	Bauch C
Co-PI:	**Krahn M**, Moghadas S
Co-I:	Deeks S, Kwong J, McGeer A, Sander B, Wu J.
2009 – 2010	$99,839
Major goals of the project:	See title
% of overlap with current application	0%

40. Model-based economic evaluation of hepatitis C treatment strategies in individuals co-infected with HIV in Canada
Canadian Institutes of Health Research (CIHR)

Principal Investiagor:	Bauch C and **Krahn M**
Co-Investigators:	Bayoumi A, Klein M, Thein HH, Wilson D
2009 – 2010	$188,120
Major goals of the project:	
% of overlap with current application	

41. Health Care, Technology and Place: A Strategic Training Initiative
Canadian Institutes of Health Research (CIHR)

Principal Investigator:	Coyte P
Co-Investigators:	Andrews G, Baecker R, Bayoumi A, Boydell K, Cameron J, Carter M, Clifford T, Colantonio A, Culyer A, Dunn J, Fernie G, Gignac M, Hoch J, Holmes D, Jadad A, **Krahn M**, Laporte A, Letourneau N, Levin L, Maki B, Mihailidis A, Miller F, Mykhalovskiy E, O'Brien-Pallas L, Rosenberg M, Upshur R.
2009 – 2015	$3,850,220
Major goals of the project:	
% of overlap with current application	

Grant No. TGF - 53911

42. Phase I of the Evidence on Tap: Expedited Knowledge Synthesis 2009
Canadian Institutes of Health Research (CIHR)

Principal Investigator:	**Krahn M**
Co-Investigators:	Cadarette S, Einarson T, Alibhai S, Pham B, Machado M,

	van der Velde G, Tomlinson G
2009	No monetary involved
Major goals of the project:	
% of overlap with current application	

43. Androgen Deprivation Therapy (ADT) in Ontario: Pattern of Care, Lifetime Costs, Model-based and Real-world cost-effectiveness
Drug Innovation Fund of the Ontario Ministry of Health and Long-Term Care

Principal Investigator:	**Krahn M**
Co-Investigators:	Bell C, Gavura S, Grootendorst P, Hodgson D, Mamdani M, Peacock S, Sawka C, Sullivan T, Trudeau M, Woodward G
2009 –2012	$304,767
Major goals of the project:	
% of overlap with current application	
Grant No. 020200	

44. Canadian Centre for Applied Research in Cancer Control (ARCC): Advancing Health Economics, Services, Policy and Ethics
BC Cancer Agency

Principal Investigator:	Hoch J, Peacock S
Co-Investigators:	Barbera L, Barer M, Berry S, Brouwers M, Browman G, Culyer T, Dobrow M, Doll R, Elwood M, Evans R, Fassbender K, Gallagher R, Gibson J, Hagen N, Harvey B, Henry D, Hodgson D, **Krahn M**, Lemieux-Charles L, McBride M, Mittman N, O'Reilly S, Ringash J, Sawka C, Sullivan T, Sutcliffe S, Upshur R
7/2009 – 6/2014	$3,600,000
Major goals of the project:	See title
% of overlap with	0%

45. Phase-specific and lifetime costs of cancer in Ontario and British Columbia
Canadian Cancer Society

Principal Investigator:	**Krahn M**
Co-Investigators:	Alibhai S, Barer M, Farahati F, Hoch J, Laporte A, Marchado M, Naglie, G, Paszat L, Peacock S, Tomlinson G
2009 – 2013	$674,546
Major goals of the project:	See title
% of overlap with current application	0%

46. Non-Medical Use of Prescription Opiod analgesics in Canada: Epidemiology, Consequences and Interventions
Canadian Institute for Health Research (CIHR)

Principal Investigator:	Fischer B
Co-Investigators	Barrett S, Bouchard M, Dell C, Fallu J, Goldman H, Goldner E, **Krahn M**, Mugford G, Paterson B, Somers J, Tyndall M

2008 - 2014	$1,249,500
Major goals of the project:	See title
% of overlap with current application	0%

47. Turning for Ulcer Reduction (TURN) Study
Ministry of Health and Long-Term Care (MoHLTC)

Principal Investigator:	**Krahn M**
Co-Investigators:	Stern A, Bergstrom N, Horn S
2008 – 2011	$507,520
Major goals of the project:	See title
% of overlap with current application	0%
Grant No. 06403A	

48. Cervical cancer screening in the era of HPV vaccination: using mathematical and economic models to guide screening policy
Canadian Institute for Health Research (CIHR)

Principal Investigator:	Bauch C, Gilca V, **Krahn M**, Mai V, McLachlin C, Pham B
Co-Investigators:	Anonychuk A, Colgan T, Howlett R, John-Baptiste A, Sander B
2008-2010	$195,617
Major goals of the project:	See title
% of overlap with current application	0%

49. Estimating treatment effects for uncommon disease using observational data in a Bayesian context. The warfarin in scleroderma-pulmonary hypertension model
Canadian Institute for Health Research (CIHR)

Principal Investigator:	Feldman B
Co-Investigators:	Granton J, Hawker G, Johnson S, **Krahn M**, Tomlinson G
2008 - 2011	$104,651
Major goals of the project:	See title
% of overlap with current application:	0%

50. Development and implementation of a Type 2 Diploma program for university graduate level students to increase Canadian capacity for assessing and monitoring the use of new and existing health technologies
Canadian Institute for Health Research (CIHR)

Principal Investigator:	Goeree R, **Krahn M**, Lynd L
Co-Investigators	Lemieux-Charles L, Marra C, O'Reilly D, Tarride J, Xie F
2008 - 2009	$5,000

51. Hip Fracture and Quality of Life Pilot Study
Medical Research Foundation

Principal Investigator:	Wang P
Co-Investigators:	Squire D, Mathews M, Buehler S, **Krahn M**, Cheung A
2008 – 2009	$10,000

Major goals of the project: See title
% of overlap with current application 0%

52. Examining quality of life and health outcomes after hip fracture in urban-rural Newfoundland: A pilot study
NL Medical Research Foundation Internal Competition
Principal Investigator: Wang P
Co-Investigators Squire D, Mathews M, Buehler S, **Krahn M**, Cheung A
2008 – 2009 $10,000
Major goals of the project: See title
% of overlap with current application 0%

53. The Cost-effectiveness of Pandemic influenza Mitigation Strategies using a Stochastic Agent Based Transmission Model
CIHR Pandemic Preparedness Res-Influenza Diagnostics, Transmission Competition
Principal Investigator: **Krahn M**
Co-Investigators: Bauch C, Kwong J, McGeer A, Raboud J.
2007 – 2010 $235,273
Major goals of the project: See title
% of overlap with current application 0%

54. Toronto Health Economics and Technology Assessment Collaborative
Ministry of Health and Long-Term Care
Principal Investigator: **Krahn M**
Co-Investigators: Alibhai S, Bayoumi A, Bauch C, Chaim B, Beyene J, Bremner K, Carcone S, Detsky A, Fowler R, Englesakis M, John-Baptiste A, Einarson T, Hoch J, Chen M, Laporte A, Mittman N, MacKeigan L, Naglie G, Naimark D, Pham B, Sander B, Thein HH, Tomlinson G, Ungar W, Urbach D.
2007 –2012 $7,069,092
Major goals of the project: See title
% of overlap with current application 0%

55. Economic Evaluation of Adjunctive Intravenous Anti-thrombotic and Anti-platelet Agents in Percutaneous Coronary Intervention for Stable Angina
Canadian Institute for Health Research (CIHR)
Principal Investigator: Wijeysundera H
Co-Investigators: **Krahn M**
2007 - 2012 $220,000
Major goals of the project: See title
% of overlap with current application 0%

56. Evaluating the need for and potential design of a no-fault compensation program for immunization related injuries
Canadian Institute for Health Research (CIHR)
Principal Investigator: Keelan J, Wilson K
Co-Investigators: Attaran A, Busse J, **Krahn M**, McGeer A, Upshur R
2007 - 2010 $145,274
Major goals of the project: See title
% of overlap with current application 0%

57. A 2-year follow-up study of the health effects of androgen deprivation therapy in men with non-metastatic Prostate cancer
Canadian Cancer Society
Principal Investigator: Alibhai S
Co-Investigators: Naglie G, **Krahn M**, Fleshner N, Duff CS, Tannock I, Tomlinson G, Warde P
2007 – 2010 $338,946
Major goals of the project: See title
% of overlap with current application 0%

58. Androgen deprivation therapy in prostate cancer patients: patterns of care, lifetime costs, and cost Effectiveness of ADT treatment
Canadian Cancer Society
Principal Investigator: **Krahn M**
Co-Investigators: Warde P, Tomlinson G, Naglie G, Alibhai S, Trachtenberg J, Laporte A, Ritvo P, Pham B
2007 – 2010 $326,774
Major goals of the project: See title
% of overlap with current application 0%

59. A 2-year follow-up study of the health effects of androgen deprivation therapy in men with non-metastatic Prostate cancer
Canadian Institute of Health Research (CIHR)
Principal Investigator: Alibhai S
Co-Investigators: Naglie G, **Krahn M**, Fleshner N
2007 – 2010 $360,000
Major goals of the project: See title
% of overlap with current application 0%

60. Evaluation of Ontario's Universal Influenza Immunization Program
Canadian Institute for Health Research (CIHR)
Principal Investigator: Guttmann A, **Krahn M**, Kwon J, Marra F, Moran M, Pourbohloul B, Reynolds d, Sander B

Co-Investigators:	Bowles S, Dell S, Garay J, Halperin S, Langley J, McNeil S, Meyers L, Northrup D, Parkin P, Patrick D, Roos L, Ross A, Smith M, Stukel T, Svenson L, To T, Upshur R
2006-2010	$843,609
Major goals of the project:	See title
% of overlap with current application	0%

61. Should Ontario's Universal Influenza Immunization Program be adopted by all Canadian provinces? A Comprehensive approach to the evaluation of influenza management policies and estimation of potential Health effects and costs
University of Toronto Research Program/Health Canada

Principal Investigator:	Raboud J
Co-Investigators:	Sander B, McGeer A, Kwong J, Maetzel A, Manuel D, **Krahn M**, Naglie G
2006 – 2009	$378,007
Major goals of the project:	See title
% of overlap with current application	0%

62. Evaluation of Ontario's Universal Influenza Immunization Program
Canadian Institute of Health Research (CIHR)

Nominated PI:	Manuel DG
Principal Investigator:	**Krahn M**, Guttmann A, Kwong J, Pourbohloul B, Langley JM, Moran MK, Sander B, Reynolds D, Marra F
Co-Investigators:	Stukel T, Smith M, Halperin S, Roos L, Upshur R, Meyers L, Garay J, Patrick D, Svenson L, Dowlatabadi H, Ross A, MacNeil S
2006 – 2009	$1,050,000
Major goals of the project:	See title
% of overlap with current application	0%

63. Population-based estimates of health care cost in persons with hepatitis C
Ministry of Health and Long-Term Care (MoHLTC)

Principal Investigator:	Paterson M
Co-Investigators:	Laupacis A, **Krahn M**
2006 – 2006	$192,140
Major goals of the project:	See title
% of overlap with current application	0%

64. Markov Models for cost effectiveness analysis: A framework for assessing external consistency
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

Principal Investigator:	**Krahn M**
Co-Investigators:	Pham B, Tricco A, Hoch J, Tomlinson G
2006 – 2007	$41,135.88
Major goals of the	See title

project:
% of overlap with current application 0%

65. Evaluation of a multi-disciplinary approach for the treatment of hepatitis C virus in injection drug users
Canadian Institute of Health Research (CIHR)
Principal Investigator: Conway B and Farley J
Co-Investigators: Fraser C, **Krahn M**, Singer J
2005 – 2008 $462,111
Major goals of the project: See title
% of overlap with current application 0%
Grant No. 135409

66. Population-based estimates of cost and quality of life in community-dwelling HCV patients.
Canadian Institutes of Health Research (CIHR)
Principal Investigator: **Krahn M**
Co-Investigators: Anis A, Heathcote J, Krajden M, Pourbohloul B, Shadmani R, Tomlinson G, Yoshida E
2005 – 2008 $455,262
Major goals of the project: See title
% of overlap with current application 0%

67. Appropriate management of neck pain: Contribution of decision analysis to the development of tre recommendations
Canadian Institute for Health Research (CIHR)
Principal Investigator: Van der Velde G
Co-Investigators: Hogg-Johnson S, **Krahn M**
2005 - 2008 $110,000
Major goals of the project See title
% of overlap with application 0%

68. Longitudinal Canadian Alzheimer's Disease quality of life study
Canadian Institute for Health Research (CIHR)
Principal Investigator: Naglie G
Co-Investigators: Bacher Y, Beattie B, Bergman H, Black S, Borrie M, Byszewski A, Freedn Hogan D, Irvine M, **Krahn M**, MacKnight C, Patterson C, Ritvo P, Strei Tomlinson G
2005 - 2007 $50,000
Major goals of the project See title
% of overlap with application 0%

69. Evaluating the cost effectiveness of a universal hepatitis A vaccination programme: a dynamic perspective
Canadian Institute of Health Research (CIHR) Industry-Partnered Grant (2/3 from GSK, 1/3 from CIHR
Principal Investigator: Bauch C
Co-Investigators **Krahn M**, Duval B, Gilca V

2005 – 2006	$19,865
Major goals of the project:	See title
% of overlap with current application	0%

70. Liquid-Based Techniques for Cervical Cancer Screening
CCOHTA

Principal Investigator:	**Krahn M**
Co-Investigators:	Rosen B, McLachlin M, Sanders B, Grootendorst P, Tomlinson G, Pham B
2005 – 2006	$61,594.55
Major goals of the project:	See title
% of overlap with current application	0%

71. Utility values for health-state outcomes to non-surgical treatments for neck pain
Ministry of Health and Long-Term Care/Ontario Chiropractors Association Research Fund

Principal Investigator:	van der Velde G
Co-Investigators:	Hogg-Johnson S, **Krahn M**, Hurwitz E, Cassidy JD, Llewellyn-Thomas H, Cote P
2005 – 2006	$68,500
Major goals of the project:	See title
% of overlap with current application	0%

72. Health-related quality of life in advanced lung disease and lung transplantation
Physicians Services Incorporated

Principal Investigator:	Singer L
Co-Investigators:	**Krahn M**, Tullis D, Granton J, Waddell T
2005 – 2008	$290,001
Major goals of the project:	See title
% of overlap with current application	0%

73. Investigating socio-behavioural risk, prevention and treatment factors for HCV in special populations
Canadian Institute for Health Research

Principal Investigator:	Fischer B
Co-Investigators	Butt G, Kerr T, **Krahn M**, Krajden M, Myers T, Paterson B, Rehm J, Wild C
2004-2008	$600,000
Major goals of the project	See title
% of overlap with application	0%

74. Age-stratified rates of 30 day morbidity and mortality after radical prostatectomy for localized prostate cancer

Canadian Institute of Health Research (CIHR)
Principal Investigator: Alibhai S
Co-Investigators: **Krahn M**, Naglie G, Tomlinson G
2004 – 2005 $75,000
Major goals of the project: See title
% of overlap with current application 0%

75. Research Training Program Grant in Hepatitis C
Canadian Institute of Health Research (CIHR)
Principal Investigator: Bilodeau M
Co-Investigators: Babiuk L, Balfour L, Bruneau J, Conway B, Edwards A, Fischer B, Gotte M, Heathcote J, Klein M, Kneteman N, **Krahn M**, Krajden M, Levy G, McGilrary I, Michalak T, Mugford G, Ostrowski M, Paterson B, Pause A, Pezacki J, Richardson C, Roberts E, Shoukry N, Sonenberg N, Tellier R, Tyndall M, Tyrrell D, Walmsley S
2003 - present $3,607,500
Major goals of the project: See title
% of overlap with current application 0%

76. Estimating costs associated with hepatitis C (HCV) infection for input into a comprehensive decision analytic policy model to inform clinical decision and policy development
CIHR Doctoral Training Fellowship
Recipient: John-Baptiste A
Supervisor: **Krahn M**
2003 – 2007 $120,000
Major goals of the project: See title
% of overlap with current application 0%

77. Developing a Canadian policcy model for hepatitis C: Estimating cost and quality of life
Canadian Institute for Health Research (CIHR)
Principal Investigator: **Krahn M**, Krajden M
Co-Investigators: Anis A, Heathcote E, Maetzel A, Naglie G, ritvo P, Sherman M, Tomlinson G
2003 - 2004 $50,340

78. Optimized molecular diagnosis for malignant hyperthermia and central core disease
Canadian Institute for Health Research (CIHR)
Principal Investigator: MacLennan D
Co-Investigators: Gallie B, Kraeva N, **Krahn M**, Loke J, Phillips M, Reid G
2003 - 2004 $100,000

79. Canadian Alzheimer's Disease Quality of Life Study
Canadian Institute for Health Research (CIHR)
Principal Investigator: Naglie G

Co-Investigators:	Tomlinson G, Hogan D, Freedman M, **Krahn M**, Irvine J, Patterson C, Borrie M, Streiner D, Black S, MacKnight C, Bergman H, Beattie L, Bacher Y, Byszewski A, Ritvo P
2002 – 2008	$779,374
Major goals of the project:	See title
% of overlap with current application	0%

80. Decision analytic and cost-effectiveness analyses of non-surgical conservative neck pain treatments (non-steroidal anti-inflammatory drugs and cervical spinal manipulation)

Canadian Institue for Health Research (CIHR)

Principal Investigator:	Van der Velde G
Co-Investigators:	Hogg-Johnson S, **Krahn M**
2002 - 2006	$157,416
Major goals of the project	See title
% of overlap with application	0%

81. A prospective, longitudinal study to examine health effects of androgen deprivation therapy on older me prostate cancer

Canadian Institutes for Health Research (CIHR)

Principal Investigator:	Alibhai S
Co-Investigators:	**Krahn M**, Naglie G, Tannock I, Duff-Canning S, Tomlinson G,
2002 – 2004	$72,127
Major goals of the	See title
% of overlap with current application	0%

82. A national hepatitis C research training program grant

Canadian Institute of Health Research (CIHR)

Principal Investigator:	Babiuk L, Edwards A, Fischer B, Heathcote E, Kneteman N, **Krahn M,** MacDonald K, Paterson B, Richardson C, Rottapel R, Sonenberg N, Tyrrell D
2002-2003	$5,000
Major goals of the project:	See title
% of overlap with current:	0%

83. Practices, Parameters, and Priorities: Operationalizing the Behaviour of the Great Attending Physician

PSI Foundation

Principal Investigator:	Tzanetos K
Co-Investigators:	**Krahn M**, Regehr G
2002 – 2003	$8,400
Major goals of the project:	See title
% of overlap with	0%

84. Large Centre Training Grant, The Canadian Prostate Cancer Research Initiative
The Prostate Cancer Group, Princess Margaret Hospital

Principal Investigator:	Tannock I
Co-Investigators:	Sherar M, Warde P, Trachtenberg J, Stewart K, **Krahn M**, Crook J, Moore M
2001 – 2006	$397,750
Major goals of the project:	See title
% of overlap with current application	0%

85. Using Policy Models to Improve Resources Allocation in Health
Canadian Institutes for Health Research (CIHR)

Principal Investigator:	**Krahn M**
2001 - 2007	$201,054
Major goals of the	See title
% of overlap with current application	0%

86. Canadian Institute of Health Research (CIHR)

Principal Investigator:	**Krahn M**
Co-Investigators:	Holowaty E, Naglie G, Irvine J, Ritvo P, Mamdani M, Alibhai S,Trachtenberg J, Laporte A
2001 – 2007	$525,661
Major goals of the project:	See title
% of overlap with	0%

87. Utility values for health state outcomes to two conservative treatments for neck pain obtained from a sample of neck pain patients and the general public: a pilot study

Ministry of Health and Long-Term Care/Ontario Chiropractic Association Research Fund

Principal Investigator:	van der velde G
Co-Investigators:	Hogg-Johnson S, **Krahn M**, Maetzel A, Naglie G
2001 – 2003	$47,500
Major goals of the project:	See title
% of overlap with	0%

88. Gender differences in in-hospital resource utilization outcomes
Canadian Institute for Health Research (CIHR)

Principal Investigator:	Cheung A
Co-Investigators:	Abrams H, Alibhai S, Bacchus C, Choudhry N, Gold W, Kapral M, **Krahn M**, Lee Y, Naglie G, Tomlinson G
2001-2002	$10,000
Major goals of the project:	See Title
% of overlap with current:	0%

89. Preference functions for a health state classification system for prostate cancer
National Cancer Institute of Canada
Principal Investigator: **Krahn M**

Co-Investigators:	Ritvo P, Naglie G, Irvine J, Trachtenberg J, Tomlinson G, Bezjak A, Warde P, Torrance G
2000 – 2003	$163,124
Major goals of the project:	See title
% of overlap with	0%

90. Preference functions for a health state classification system for prostate cancer
Medical Research Council of Canada/CIHR

Principal Investigator:	**Krahn M**
Co-Investigators:	Ritvo P, Naglie G, Irvine J, Trachtenberg J, Tomlinson G, Bezjak A, Warde P, Torrance G
1999 - 2001	$58,197
Major goals of the project:	See title
% of overlap with	0%

91. Examination of the cost-effectiveness of Cyclo-oxgenase-2 (COX2) inhibitors
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

Principal Investigator:	Maetzel A
Co-Investigators:	**Krahn M**, Bombardier C
1999 – 2000	$25,000
Major goals of the project:	See title
% of overlap with	0%

92. Canadian Network for vaccines and immunotherapeutics of cancer and chronic viral disease (CANVAC)

National Centre of Excellence

Principal Investigator:	Ritvo P
Co-Investigators:	**Krahn M**, Irvine J, Fong G, Llewellyn-Thomas H, O'Connor A
Industry	$89.65M
NCE	$33.6M
Social Sciences Research Theme	$755,291
Major goals of the project:	See title
% of overlap with	0%

93. Do age, comorbidity and are of residence influence the treatment of prostate cancer?
The Physicians' Services Incorporated Foundation

Principal Investigator:	Alibhai S
Co-Investigators:	**Krahn M**, Cohen M, Fleshner N, Naglie G
1999 – 2000	$13,000
Major goals of the project:	See title
% of overlap with	0%

94. Comparison of population-weighted generic utility instruments to direct utility assessment in prostate Cancer patients

Medical Research Council of Canada

Principal Investigator:	**Krahn M**
Co-Investigators:	Naglie G, Irvine J, Trachtenberg J
1997	$51,442
1998 – 2000	$61,572
Major goals of the project:	See title
% of overlap with	0%

95. Arthur Bond Fellowship for Innovation Health Systems Research

Physicians' Services Incorporated Foundation (Career Award)

Recipient:	**Krahn M**
1996 – 1997	$50,000
1997 – 1998	$50,000
Major goals of the project:	See title
% of overlap with	0%

96. An economic evaluation of Synsorb-PK for the prevention of HUS in children

Medical Research Council of Canada (MRC)

Principal Investigator:	Klassen T
Co-Investigators:	**Krahn M**, Capelli M, Orrbine E
1996 – 1997	$51,400
1997 – 1998	$26,700
Major goals of the project:	See title
% of overlap with	0%

97. Development and validation of a utility instrument for prostate cancer

National Cancer Institute

Principal Investigator:	**Krahn M**
Co-Investigators:	Ritvo P, Naglie G, Irvine J, Trachtenberg J
1994 – 1997	$48,100
Major goals of the project:	See title
% of overlap with	0%

Non-Peer Reviewed

1. Update of National Hepatitis C Prognostic Compensation Model

Hepatitis C Plaintiffs, Federal Provincial, and Territorial Governments of Canada

Principal Investigator:	**Krahn M**
Co-Investigators:	Locke K, Heathcote J, Scully L
2008 - 2009	$192,000

2. Roche Modeling Fellowship

Hoffman-LaRoche Canada
Recipient: **Krahn M**
2008 - $50,000/year

3. Update of National Hepatitis C Prognostic Compensation Model
Hepatitis C Plaintiffs, Federal Provincial, and Territorial Governments of Canada
Principal Investigator: **Krahn M**
Co-Investigators: Locke K, Heathcote J, Scully L
2004 – 2005 $196,645

4. Decision analysis of non-surgical treatment for neck pain
Canadian Chiropractic Protective Agency
Principal Investigator: van der Velde G
Co-Investigators: **Krahn M**, Hogg-Johnson S, Cassidy JD, Llewellyn-Thomas H, Cote P
2003 – 2006 $88,000

5. Cost-effectiveness of a decompression chamber for use in the international space station
Canadian Space Agency
Principal Investigator: **Krahn M**
Co-Investigators: Gray G, Straus S, Naglie G, Sackett D
2002 – 2003 $96,145

6. Update of National Hepatitis C Prognostic Compensation Model
Hepatitis C Plaintiffs, Federal Provincial, and Territorial Governments of Canada
Principal Investigator: **Krahn M**
Co-Investigators: Locke K, Heathcote J, Scully L
2000 – 2002 $196,645

7. Cost-effectiveness of universal hepatitis A vaccination
Health Canada
Principal Investigator: **Krahn M**
03/2000 – 06/2001 $25,000

8. Comparison of generic and disease specific preference instruments
Zeneca Pharma
Principal Investigator: **Krahn M**
Co-Investigators: Ritvo P, Naglie G, Irvine J, Trachtenberg J
06/2001 – 07/2002 $20,000
06/2000 – 07/2001 $20,000
06/1999 – 06/2000 $20,000

9. Developing a natural history model of HCV infection
   Canadian Association for the study of the liver
   Principal Investigator: **Krahn M**
   Co-Investigators: Seeff L, Wong J, Heathcote J
   01/1999 – 12/1999 $75,000

10. Health and economic effects of PSA screening in Canada
    National Cancer Institute of Canada
    Principal Investigator: **Krahn M**
    1999 $10,000

11. Economic evaluation of chemotherapy with Mitoxantrone Plus Prednisone for symptomatic hormone Resistant prostate cancer
    Immunex Inc.
    Principal Investigator: Tannock I
    Co-Investigators: **Krahn M**, Bloomfiel D
    06/1996 – 06/1997 $108,464

12. Direct and indirect costs of asthma in Canada
    Glaxo Canada
    Principal Investigator: **Krahn M**
    Co-Investigators: Detsky A
    1992 – 1993 $20,000

13. Cost-effectiveness of universal vaccination of grade six students in British Columbia with Hepatitis B Vaccine
    SmithKline Beecham Canada
    Principal Investigator: **Krahn M**
    1991 – 1992 $22,500

Patents Awarded

None

PUBLICATIONS:

Published

1. Fergenbaum J, Bermingham S, **Krahn M**, Alter D, Demers C. Care in the home for the Management of chronic heart failure. Systematic review and cost-effectiveness analysis. Journal of Cardiovascular Nursing. 2015 [Epub ahead of print].
2. Wong WW, Tu HA, Feld JJ, Wong T, **Krahn M**. Cost-effectiveness of screening for hepatitis C in Canada. CMAJ. 2015 Jan 12. pii:cmaj.140711. [Epub ahead of print]. PMID: 25583667
3. Fowler R, Mittmann N, Geerts W, Heels-Ansdell D, Gould M, Guyatt G, **Krahn M**, Finfer S, Pinto R, chan B, Ormanidhi O, Arabi Y, Qushmaq I, Rocha M, Dodek P, McIntyre L, Hall R, Ferguson N, Mehta S, Marshall J, Doig C, Muscedere J, Jacka M, Klinder J, Vlahakis N, Orford N, Seppelt I, Skrobik Y, Sud S, Cade J, Cooper J, Cook D. Economic evaluation of the prophylaxis for thromboembolism in critical care trial (E-PROTECT): study protocol for a randomized controlled trial. Trials.2014 Dec 20;15(1):502.[Epub ahead of print]. PMID: 25528663
4. Abrahamyan L, Wong J, Pham B, Trubiani G, Carcone S, Mitsakakis N, Rosen L, Rac V, **Krahn M**. Structure and characteristics of community-based multidisciplinary wound care teams in Ontario: An environmental scan. Wound Repair Regen. 2014 Nov 25. doi:10.1111/wrr.12241.[Epub ahead of print]. PMID: 25421743
5. Fowler R, Mittmann N, Geerts W, Heels-Ansdell D, Gould M, Guyatt G, **Krahn M**, Finfer S, Pinto R, Chan B, Ormanidhi O, Arabi Y, Qushmaq I, Rocha M, Dodek P, McIntyre L, Hall R, Ferguson N, Mehta S, Marshall J, Doig C, Muscedere J, Jacka M, Klinger J, Vlahakis N, Orford N, Seppelt I, Skrobik Y, Sud S, Cade J, Cooper J, Cook D, Canadian Critical Care Trials Group; Australia and New Zealand Intensive Care Society Clinical Trials Group. Cost-effectiveness of dalteparin vs unfractionated heparin for the prevention of venous thromboembolism in critically ill patients. JAMA. 2014 Nov 26;312(20):2135-45.doi:10.1001/jama.2014.15101. PMID: 25362228
6. **Krahn M**. Prostate cancers screening: going beyond the clinical evidence. CMAJ. 2014 Nov 4;186(16):1201-2. doi: 10.1503/cmaj.141252. Epub 2014 Oct 27. PMID: 25349002
7. Micieli A, Bennell MC, Pham B, **Krahn M**, Singh SM, Wijeysundera HC. Identifying future research priorities using value of information analyses: left atrial appendage occlusion devices in atrial fibrillation. J Am Heart Assoc. 2014 Sep 16;3(5):e001031.doi:101.1161/JAHA.114.001031. PMID: 25227405
8. Tu HA, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, Kwong JC, Coyte PC, **Krahn M**, Sander B. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. Vaccine. 2014 Aug 12. pii:S0264-410X(14)01078-0. doi:10.1016/j.vaccine.2014.07.085.[Epub ahead of print] PubMed PMID: 25131732.
9. Khor S, Beca J, **Krahn M**, Hodgson D, Lee L, Crump M, Bremner KE, Luo J, Mamdani M, Bell CM, Sawka C, Gavura S, Sullivan T, Trudeau M, Peacock S, Hoch JS. Real world costs and cost-effectiveness of Rituximab for diffuse large B-cell lymphoma patients: a population-based analysis. BMC Cancer. 2014 Aug 12:14:586. doi:10.1186/1471-2407-14-586. PubMed PMID: 25117912; PubMed Central PMCID: PMC4148552.
10. de Oliveira C, Bremner KE, Pataky R, Gunraj N, Haq M, Chan K, Cheung WY, Hoch JS, Peacock S, **Krahn M**. Trends in use and cost of initial cancer treatment in Ontario: a population-based descriptive study. CMAJ Open. 2013 Dec 9;1(4):E151-8. doi:10.9778/cmajo.20130041. eCollection 2013 Oct. PubMed PMID: 25077117; PubMed Central PMCID: PMC3986020.
11. Pham B, Tu HA, Han D, Pechlivanoglou P, Miller F, Rac V, Chin W, Tricco A, Paulden M, Bielecki J, **Krahn M**. Early economic evaluation of emerging health technologies: protocol of a systematic review. Systematic Reviews 2014;3:81-8. doi: 10.1186.2046-4053-3-81. PubMed PMID: 25055987; PubMed Central PMCID: PMC4114797.
12. Langley JM, **Krahn M**, Husereau D, Spika J, Fisman DN, Chit A, Van Exan R. Incorporating economic evaluation into immunization decision making in Canada: a workshop. Expert Rev Vaccines. 2014 Jul23:1-6. [Epub ahead of print] PubMed PMID: 25052459.
13. Tadrous M, Wong L, Mamdani MM, Juurlink DN, **Krahn M**, Lévesque LE, Cadarette SM Comparative

gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis-reply to Pazianas and Abrahamsen. Osteoporos Int. 2014 Jul 18. [Epub ahead of print] PubMed PMID: 25035138

14. **Krahn MD**, Bremner KE, Luo J, Alibhai SM. Health care costs for prostate cancer patients receiving androgen deprivation therapy: Treatment and adverse events. Curr Oncol. 2014 Jun;21(3):e457-65. doi: 10.3747/co.21.1865. PubMed PMID: 24940106; PubMed Central PMCID: PMC4059810.
15. Azarpazhooh A, Dao T, Ungar W, Chaudry F, Figueiredo R, **Krahn M**, Friedman S. Clinical decision making for a tooth with apical periodontitis: the patients' preferred level of participation. J Endod. 2014 Jun;40(6):784-9. doi: 10.1016/j.joen.2014.01.045. Epub 2014 Mar 29. PubMed PMID: 24862704.
16. Avila M, Pardo Y, Castells M, Ferrer F, Boladeras A, Pera J, Prada P, Guiz B, de Paula B, Hernandez H, Pont A, Alonso J, Garin O, Bremner K, **Krahn M**, Ferrer M; The Multicentric Spanish Group of Clinically Localized Prostate Cancer. Adaptation and validation of the Spanish version of the Patient-Oriented Prostate Utility Scale (PORPUS). Qual Life Res. 2014 May 1 [Epub ahead of print] PubMed PMID: 24789667.
17. Perlis N, **Krahn M**, Alibhai S, Finelli A, Ritvo P, Bremner KE, Kulkarni G. Conceptualizing global health-related quality of life in bladder cancer. Qual Life Res. 2014 Oct;23(8):2153-67. doi: 10.1007/s11136-014-0685-9. Epub 2014 Apr 13. PubMed PMID: 24729055.
18. **Krahn M**, Bremner KE, Zagorski B, Alibhai SM, Chen W, Tomlinson G, Mitsakakis N, Naglie G. Health Care Costs for State Transition Models in Prostate Cancer. Med Decis Making. 2014 Apr; 34(3): 366-78
19. Molinari M, De Coutere S, **Krahn M**, Helton S, Urbach DR. Patients' preferences and trade-offs for the treatment of early stage hepatocellular carcinoma. J Surg Res. 2014 Jun 1;189(1):57-67. doi: 10.1016/j.jss.2014.02.015. Epub 2014 Feb 15. PubMed PMID: 24650457.
20. Matthew AG, Alibhai SMH, Davidson T, Currie KL, Jiang H, **Krahn M**, Fleshner NE, Kalnin R, Louis AS, Davison BJ, Trachtenberg J. Health-related quality of life after radical prostatectomy: Long-term outcomes. Qual Life Res. 2014Oct;23(8):2309-17. doi: 10.1007/s11136-014-0664-1. Epub 2014 Mar 9. PubMed PMID: 24609438.
21. Wong WW, **Krahn M**. Screening for HCV. CMAJ. 2014 Mar 4;186(4):294. doi: 10.1503/cmaj.114-0016. PubMed PMID:24591492; PubMed Central PMCID: PMC3940579.
22. Djalalov S, Beca J, Hoch JS, **Krahn M**, Tsao MS, Cutz JC, Leighl NB. Cost Effectiveness of EML4-ALK Fusion Testing and First-Line Crizotinib Treatment for Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer. J Clin Oncol. 2014 Apr 1;32(10):1012-9. doi: 10.1200/JCO.2013.53.1186. Epub 2014 Feb 24. PubMed PMID: 24567430.
23. Burton K, Perlis N, Aviv R, Moody A, Kapral M, **Krahn M**, Laupacis A. Systematic Review, Critical Appraisal, and Analysis of the Quality of Economic Evaluations in Stroke Imaging. Stroke. 2014 Mar;45(3):807-14. doi: 10.1161/STROKEAHA.113.004027. Epub 2014 Feb 11. Review. PubMed PMID: 24519409.
24. Stern A, Mitsakakis N, Paulden M, Alibhai S, Wong J, Tomlinson G, Brooker AS, **Krahn M**, Zwarenstein M. Pressure ulcer multidisciplinary teams via telemedicine: a pragmatic cluster randomized stepped wedge trial in long term care. BMC Health Serv Res. 2014 Feb 24;14(1):83. doi: 10.1186/1472-6963-14-83. PubMed PMID: 24559218; PubMed Central PMCID: PMC4104322.
25. Wijeysundera HC, Austin PC, Wang X, Bennell MC, Abrahamyan L, Ko DT, Tu JV, **Krahn M**. The Effect of Multidisciplinary Heart Failure Clinic Characteristics on 1-Year Postdischarge Health Care Costs: A Population-based Study. Med Care. 2014 Mar;52(3):272-9. doi: 10.1097/MLR.0000000000000071. PubMed PMID: 24509362.
26. Naimark DM, Kabboul NN, **Krahn M**. Response to "The Life Table Method of Half-Cycle Correction: Getting It Right" Med Decis Making. 2014 Apr:34(3):286-7. doi: 10.1177/0272989X14520719. Epub 2014 Jan 22. PubMed PMID: 24452200.
27. Treloar C, Rance J, Dore GJ, Grebely J, ETHOS Study Group. Barriers and facilitators for assessment and treatment of hepatitis C virus infection in the opioid substitution treatment setting: Insights from the ETHOS study. J Viral Hepat. 2014 Aug; 21(8):560-7. doi:10.1111/jvh.12183. Epub 2013 Dec 3. PubMed PMID: 24299222.
28. Tadrous M, Wong L, Mamdani MM, Juurlink DN, **Krahn M**, Lévesque LE, Cadarette SM Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis-reply to

Pazianas and Abrahamsen. Osteoporos Int. 2014 Apr;25(4):1225-35. doi: 10.1007/s00198-013-2576-2. Epub 2013 Nov 28. PubMed PMID: 24287510.

29. Azarpazhooh A, Dao T, Figueiredo R, **Krahn M**, Friedman S. A survey of patients' preferences for the treatment of teeth with apical periodontitis. J Endod. 2013 Dec;39(12):1534-41. doi: 10.1016/j.joen.2013.07.012. Epub 2013 Sep 6. PubMed PMID: 24238442.
30. Grebely J, Bilodeau M, Feld JJ, Bruneau J, Fischer B, Raven JF, Roberts E, Choucha N, Myers RP, Sagan SM, Wilson JA, Bialystok F, Tyrrell DL, Houghton M, Krajden M, National CIHR Research Training Program in Heaptitis C. The Second Canadian Symposium on hepatitis C virus: a call to action. Can J Gastroenterol. 2013 Nov;27(11):627-32. PubMed PMID: 24199209; PbMed Central PMCID: PMC3816942.
31. Health Quality Ontario. Screening and management of depression for adults with chronic diseases: an evidence-based analysis. Ont Health Technol Assess Ser. 2013 Sept 1;13(8):1-45. eCollection 2013. Review. PubMed PMID: 24133570.
32. **Krahn M**, Bremner KE, Alibhai SMH, Ni A, Tomlinson G, Laporte A, Naglie G. A reference set of health utilities for long-term survivors of prostate cancer: population-based data from Ontario, Canada. Qual Life Res 2013; 22(10): 2951-2962
33. Bremner KE, Mitsakakis N, Wilson L, **Krahn M.** Predicting utility scores for prostate cancer: mapping the Prostate Cancer Index to the Patient-Oriented Prostate Utility Scale (PORPUS). Prostate Cancer Prostatic Dis. 2013 Oct 15. doi: 10.1038/pcan.2013.44. [Epub ahead of print]
34. Wijeysundera HC, Tomlinson G, Ko DT, Dzavik V, **Krahn M.** Medical Therapy v. PCI in Stable Coronary Artery Disease: A Cost-Effectiveness Analysis. Med Decis Making. 2013 Oct;33(7):891-905. doi: 10.1177/0272989X13497262. Epub 2013 Jul 25.
35. Naimark DM, Kabboul NN, **Krahn M**. The half-cycle correction revisited: redemption of a kludge. Med Decis Making. 2013 Oct;33(7):961-70. doi: 10.1177/0272989X13501558.
36. Cantor SB, Deshmukh AA, **Krahn M**, Volk RJ. Use of forecasted assessment of quality of life to validate time-tradeoff utilities and a prostate cancer screening decision-analytic model. Health Expect. In press.
37. Azarpazhooh A, Dao T, Figueiredo R, **Krahn M**, Friedman S. A survey of dentists' preferences for the treatment of teeth with Apical Periodontitis. J Endod. 2013 Oct;39(10):1226-1233. doi: 10.1016/j.joen.2013.06.023.
38. Azarpazhooh A, Dao T, Figueiredo R, **Krahn M**, Friedman S. A survey of patients' preferences for the treatment of teeth with apical periodontitis. J Endod. 2013 Dec;39(12):1534-41. doi: 10.1016/j.joen.2013.07.012. Epub 2013 Sep 6.
39. de Oliveira C, Nguyen H, Wijeysundera H, Wong W, Woo G, Grootendorst P, Liu P, **Krahn M**. Estimating the payoffs from cardiovascular disease research in Canada: an economic analysis. CMAJ Open. 2013 Jul 25;1(2)e83-90. DOI: 10.9778/cmajo.20130003. ecollection 2013 May. PubMed PMID: 25077108.
40. Mitsakakis N, Wijeysundera HC, **Krahn M**. Beyond case fatality rate: using potential impact fraction to estimate the effect of increasing treatment uptake on mortality. BMC Med Res Methodol. 2013 Sep 4;13(1):109. [Epub ahead of print]
41. de Oliveira C, Bremner KE, Ni A, Alibhai SM, Laporte A, **Krahn M**. Patient time and out-of-pocket costs for long-term prostate cancer survivors in Ontario, Canada. J Cancer Surviv. 2013 Aug 23. [Epub ahead of print]
42. Lipscomb J, Yabroff KR, Hornbrook MC, Gigli A, Francisci S, **Krahn M**, Gatta G, Trama A, Ritzwoller DP, Durand-Zaleski I, Salloum R, Chawla N, Angiolini C, Crocetti E, Giusti F, Guzzinati S, Mezzetti M, Miccinesi G, Mariotto A. Comparing cancer care, outcomes, and costs across health systems: charting the course. J Natl Cancer Inst Monogr. 2013;2013(46):124-30. doi: 10.1093
43. Paulden M, Franek J, Pham B, Bedard PL, Trudeau M, **Krahn M**. Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer. Value Health. 2013 Jul-Aug;16(5):729-39. doi: 10.1016/j.jval.2013.03.1625. Epub 2013 Jul 1.

44. Alavi M, Grebely J, Micallef M, Dunlop AJ, Balcomb AC, Day CA, Treloar C, Bath N, Haber P, Dore G; Enhancing Treatment for hepatitits C in Opioid Substitution Settings (ETHOS) Study Group. Clin Infect Dis. 2013 Aug; 57 Suppl 2:S62-9. doi: 10.1093/cid/cit305. PubMed PMID: 23884068.
45. Chan B, Ieraci L, Mitsakakis N, Pham B, **Krahn M**. Net costs of hospital-acquired and pre-admission PUs among older people hospitalised in Ontario. J Wound Care. 2013 Jul;22(7):341-2, 344-6.
46. Brooker AS, Carcone S, Witteman W, **Krahn M**. Quantitative patient preference evidence for health technology assessment: a case study. Int J Technol Assess Health Care. 2013 Jul;29(3):290-300. doi: 10.1017/S0266462313000329.
47. Chit A, Parker J, Halperin SA, Papadimitropoulos M, **Krahn M**, Grootendorst P. Toward more specific and transparent research and development costs: The case of seasonal influenza vaccines. Vaccine. 2013 Jul 3. doi:pii: S0264-410X(13)00847-5. 10.1016/j.vaccine.2013.06.055. [Epub ahead of print]
48. Nguyen VH, Oliverira C, Wijeysundera H, Wong WWL, Woo G, Grootendorst P, Liu P, **Krahn M**. Canada's Contribution to Global Research in Cardiovascular Diseases. The Canadian Journal of Cardiology. 2013; 29(6):742-746.
49. Wong W W L, Woo G, Heathcote JE, **Krahn M**. Disease burden of chronic hepatitis B among Immigrants in Canada. Canadian Journal of Gastroenterology. 2013; 27(3):137-147.
50. Abrahamyan L, Trubiani G, Witteman W, Mitsakakis N, **Krahn M**, Wijeysundera HC: Insights Into the Contemporary Management of Heart Failure in Specialized Multidisciplinary Ambulatory Clinics, Can J Cardiol. 2013 Sept;29(9):1062-8
51. Alibhai SM, Mohamedali HZ, Gulamhusein H, Panju AH, Breunis H, Timilshina N, Fleshner N, **Krahn MD**, Naglie G, Tannock IF, Tomlinson G, Warde P, Duff Canning S, Cheung AM. Changes in bone mineral density in men starting androgen deprivation therapy and the protective role of vitamin D. Osteoporos Int. 2013 Apr 6.
52. Nikitovic M, Wodchis WP, **Krahn M**, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. Osteoporos Int. 2013 Feb;24(2):659-69.
53. Thein HH, Isaranuwatchai W, Campitelli MA, Feld JJ, Yoshida E, Sherman M, Hoch JS, Peacock S, **Krahn M**, Earle CC. Health care costs associated with hepatocellular carcinoma: A population-based study. Hepatology. 2013 Oct;58(4):1375-84
54. Wijeysundera HC, Trubiani G, Wang X, Mitsakakis N, Austin PC, Ko DT, Lee DS, Tu JV, **Krahn M**. A population-based study to evaluate the effectiveness of multidisciplinary heart failure clinics and identify important service components. Circ Heart Fail. 2013 Jan;6(1):68-75.
55. Paulden M, Franek J, Pham B, Bedard PL, Trudeau M, **Krahn M.** Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer. Value Health. 2013 Jul-Aug;16(5):729-39. doi: 10.1016/j.jval.2013.03.1625. Epub 2013 Jul 1.
56. de Oliveira C, Wijeysundera HC, Tobe SW, Lum-Kwong MM, Von Sychowski S, Wang X, Tu JV, **Krahn M**. Economic analysis of Heart and Stroke Foundation of Ontario's hypertension management initiative. Clinicoecon Outcomes Res. 2012;4:323-36. Epub 2012 Nov 13.
57. Fukada C, Kohler JC, Boon H, Austin Z, **Krahn M**. Prescribing gabapentin off label: Perspectives from pychiatry, pain and neurology specialists. Can Pharm J (Ott). 2012 Nov;145(6):280-284
58. Tsui TC, Boon H, Boecker A, Kachan N, **Krahn M**. Understanding the role of scientific evidence in consumer evaluation of natural health products for osteoarthritis - an application of the means end chain approach. BMC Complement Altern Med. 2012 Oct 30;12:198.
59. Mittmann N, Koo M, Danerman N, McDonald A, Baker M, Matlow A, **Krahn M**, Shojania KG, Etchells E. The economic burden of patient safety targets in acute care: a systematic review. Drug Healthc Patient Saf. 2012;4:141-65. Epub 2012 Oct 5.
60. OHTAC COPD Collaborative. Chronic obstructive pulmonary disease (COPD) evidentiary framework. Ont Health Technol Assess Ser. 2012;12(2):1-97. Epub 2012 Mar 1.
61. John-Baptiste A, Yeung MW, Leung V, van der Velde G, **Krahn M**. Cost effectiveness of hepatitis C-related interventions targeting substance users and other high-risk groups: a systematic review. Pharmacoeconomics. 2012 Nov 1;30(11):1015-34.
62. Roberts M, Russell LB, Paltiel AD, chambers M, McEwan P, **Krahn M**, ISPOR-SMDM Modeling Good Research Practices Task Force. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good

Research Practices Task Force -2. Value Health. 2012 Sept-Oct;15(6):804-11

63. Roberts M, Russell LB, Paltiel AD, chambers M, McEwan P, **Krahn M**, ISPOR-SMDM Modeling Good Research Practices Task Force. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force -2. Med Decis Making. 2012 Sept Oct;32(5):678-89
64. de Oliveira C, Nguyen VH, Wijeysundera HC, Wong WW, Woo G, Liu PP, **Krahn M**. How much are we spending? The estimation of research expenditures on cardiovascular disease in Canada. BMC Health Serv Res. 2012 Aug 28;12:281
65. Wijeysundera HC, Trubiani G, Abrahamyan L, Mitsakakis N, Witteman W, Paulden M, van der Velde G, Kingsbury K, **Krahn M**. Specialized multi-disciplinary heart failure clinics in Ontario, Canada: an environmental scan. BMC Health Serv Res. 2012 Aug 3;12:236
66. Jembere N, Campitelli MA, Sherman M, Feld J, Lou W, Peacock S, Yoshida E, **Krahn M**, Earle C, Thein HH. Influence of socioeconomic status on survival of hepatocellular carcinoma in the Ontario population; a population-based study, 1990-2009. PLoS One. 2012;7(7):e40917. Epub 2012 Jul 13.
67. Woo G, Tomlinson G, YimC, Lilly L, Therapondos G, Wong DK, Ungar WJ, Einarson TR, Sherman M, Heathcote JE, **Krahn M**. Health State utilities and quality of life in patients with hepatitis B. Can J Gastroenterol. 2012 Jul:26(7):445-51.
68. Chen W, Tomlinson G, **Krahn M**, Heathcote J. Immigrant patients with chronic hepatitis C and advanced fibrosis have a higher risk of hepatocellular carcinoma. J Viral Hepat. 2012 Aug;19(8):574-80. Epub 2012 Feb 1.
69. Wijeysundera HC, Wang X, Tomlinson G, Ko DT, **Krahn M**. Techniques for estimating health care costs with censored data: an overview for the health services researcher. Clinicoecon Outcomes Res. 2012;4:145-55. Epub 2012 Jun 1.
70. Zurawska U, Hicks LK, Woo g, Bell CM, **Krahn M**, Chan KK, Feld JJ. Hepatitis B virus screening before chemotherapy for lymphoma: A cost-effectiveness analysis. J Clin Oncol. 2012 Sep 10;30(26):3167-73. 2012 Jun 18.
71. Lee L, Crump M, Khor S, Hoch JS, Luo J, Bremner K, **Krahn M**, Hodgson DC. Impact of rituximab on treatment outcomes of patients with diffuse large b-cell lymphoma: a population-based analysis. Br J Haematol. 2012 Aug;158(4):481-8.
72. Mittmann N, Evans WK, Rocchi A, Longo CJ, Au HJ, Husereau D, Leighl NB, Isogai PK, **Krahn M**, Peacock S, Marshall D, Coyle D, Taylor SC, Jacobs P, Oh Pl. Guidelines for health technologies: specific guidance for oncology products in Canada. Value health. 2012 May;15(3):580-5.Epub 2012 Feb 16.
73. Etchells E, Koo M, Daneman N, McDonald A, Baker M, Matlow A, **Krahn M**, Mittmann N. Comparative economic analyses of patient safety improvement strategies in acute care: a systematic review. BMJ Qual Saf. 2012 Jun;21(6):448-56.
74. Chan KK, Siu E, **Krahn M**, Imrie K, Alibhai SM. Cost-utility analysis of primary prophylaxis versus secondary prophylaxis with granuloctye colony-stimulating factor in elderly patients with diffuse aggressive lymphoma receiving curative-intent chemotherapy. J Clin Oncol. 2012 Apr 1;30(10):1064-71. Epub 2012 Mar 5.
75. Bayoumi AM, **Krahn M**. The future of health technology assessment. Med Decis Making. 2012 Jan-Feb;32(1):7-8.
76. Federico CA, Hsu PC, Krajden M, Yoshida EM, Bremner KE, Weiss AA, Anderson FH, **Krahn M**. Patient time costs and out-of-pocket costs in hepatitis C. Liver Int. 2012 May;32(5):815-25. Epub 2012 Jan 3.
77. Pham B, Stern A, Chen W, Sander B, John-Baptiste A, Thein HH, Gomes T, Wodchis W, Bayoumi A, Machado M, Carcone S, **Krahn M**. Preventing pressure ulcers in long-term care: a cost-effectiveness analysis. Arch Intern Med. 2011 Nov 14;171(20):1839-47. Epub 2011 Sep 26.
78. Naglie G, Black S, MacKnight C, Patterson C, Hogan D, Beattie L, Borrie M, Freedman M, **Krahn M**, Bergman H, Streiner D, Ritvo P, Kowgier M, Tomlinson G. Predictors of family caregiver ratings of patient quality of life in alzheimer's disease: Cross-sectional results from the Canadian alzheimer's Disease Quality of Life (CADQOL) Study. American Journal of Geriatric Psychiatry 2011;19(10):891-901

79. Naglie G, Black S, MacKnight C, Patterson C, Hogan D, Beattie L, Borrie M, Freedman M, **Krahn M**, Bergman H, Streiner D, Ritvo P, Kowgier M, Tomlinson G. Predictors of patient self-ratings of quality of life in Alzheimer's disease: Cross-sectional results from the Canadian Alzheimer's Disease Quality of Life (CADQOL) Study. American Journal of Geriatric Psychiatry 2011;19(10):881-890
80. Wijeysundera H, Mitsakakis N, Witteman W, Paulden M, van der Velde G, Tu J, Lee D, goodman S, Petrella R, O'Flaherty M, Capewell S, **Krahn M**. Achieving quality indicator benchmarks and potential impact on coronary heart disease mortality. Can J Cardiol. 2011 Nov-Dec;27(6):756-62. Epub 2011 Sep 14.
81. Mah CL, Deber RB, Guttmann A, McGeer A, **Krahn M**. Another Look at the Human Papillomavirus Vaccine Experience in Canada. Am J Public Health. 2011 Oct;101(10):1850-7. Epub 2011 Aug 18.
82. Pham B, Teague L, Mahoney J, Goodman L, Paulden M, Poss J, Li J, Ieraci L, Carcone S, **Krahn M**. Early Prevention of Pressure Ulcers Among Elderly Patients Admitted Through Emergency Departments: A Cost-effectiveness Analysis. Ann Emerg Med. 2011 Nov;58(5):468-78 e3. Epub 2011 Aug 5
83. Wong WW, Woo G, Jenny Heathcote E, **Krahn M**. Cost effectiveness of screening immigrants for hepatitis B. Liver Int. 2011:8(31);1179-1190. Epub 2011 Jun 14.
84. Pham B, Teague L, Mahoney J, Goodman L, Paulden M, Poss J, Li J, Sikich NJ, Lourenco R, Ieraci L, Carcone S, **Krahn M**. Support surfaces for intraoperative prevention of pressure ulcers in patients undergoing surgery: a cost-effectiveness analysis. Surgery. 2011 Jul;150(1):122-32. Review.
85. Hsu PC, Federico CA, Krajden M, Yoshida EM, Bremner KE, Anderson FH, Weiss AA, **Krahn MD**. Health Utilities and Psychometric Quality of Life in Patients With Early- and Late-Stage Hepatitis C Virus Infection. J Gastroenterol Hepatol. 2012;27:149-157.
86. Tomlinson G, Bremner KE, Ritvo P, Naglie G, **Krahn M**. Development and Validation of a Utility Weighting Function for the Patient-Oriented Prostate Utility Scale (PORPUS). Med Decis Making. 2012 Jan-Feb;32(1):11-30. Epub 2011 Jun 8.
87. Warren JL, Barbera L, Bremner KE, Yabroff KR, Hoch JS, Barrett MJ, Luo J, **Krahn M**. End-of-life care for lung cancer patients in the United States and Ontario. J Natl Cancer Inst. 2011 Jun 8;103(11):853-62. Epub 2011 May 18.
88. Mah CL, Guttmann A, McGeer A, **Krahn M**, Deber RB. Compulsory school-entry vaccination laws and exemptions: who is opting out in ontario and why does it matter? Healthc Policy. 2010 May;5(4):37-46.
89. Anonychuk A, **Krahn M**. Health economic and infectious disease modelling: a guide to merging streams. Pharmacoeconomics. 2011 May;29(5):367-9.
90. Myles A, Mugford GJ, Zhao J, **Krahn M**, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol. 2011 Mar;25(3):135-9.
91. Levin L, Goeree R, Levine M, **Krahn M**, Easty T, Brown A, Henry D. Coverage with evidence development: the Ontario experience. Int J Technol Assess Health Care. 2011 Apr;27(2):159-68. Review.
92. **Krahn M**, Bremner KE, Tomlinson G, Luo J, Ritvo P, Naglie G, Alibhai SM. Androgen deprivation therapy in prostate cancer: are rising concerns leading to falling use? BJU Int. 2011 Nov;108(10):1588-96. Epub 2011 Mar 31.
93. Pham B, Chen MH, Tricco AC Ms, Anonychuk A, **Krahn M**, Bauch CT. Use of a Catalytic Model to Estimate Hepatitis A Incidence in a Low-Endemicity Country: Implications for Modeling Immunization Policies. Med Decis Making. 2012 Jan-Feb;32(1):167-75. Epub 2011 Mar 10.
94. Machado M, O'Brodovich R, Krahn M, Einarson TR. International drug price comparisons: quality assessment. Rev Panam Salud Publica, 2011 Jan;29(1):46-51
95. Wijeysundera H. C, Tomlinson G, Norris CM, Ghali WA, Ko DT, **Krahn M**. Predicting EuroQol EQ-5D Utility Scores from the Seattle Angina Questionnaire in Coronary Artery Disease: A Mapping Algorithm using a Bayesian Framework. Medical Decision Making 2011 May-Jun;31(3)481-93.
96. Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, **Krahn M**. Health Care Costs Associated with Hepatitis C: A Longitudinal Cohort Study. Can J Gastroenterol. 2010 Dec; 24(12):717-26.
97. Wijeysundera HC, Machado M, Wang X, Van Der Velde G, Sikich N, Witteman W, Tu JV, Lee DS, Goodman SG, Petrella R, O'Flaherty M, Capewell S, **Krahn M**. Cost-effectiveness of specialized multidisciplinary heart failure clinics in Ontario, Canada. Value Health. 2010 Dec; 13(8):915-21. Epub

2010 Nov 23.

98. Alibhai SM, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, **Krahn, M**, Fleshner NE, Warde P, Canning SD, Klotz L, Naglie G. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. J Clin Oncol. 2010 Dec 1; 28(34):5038-45. Epub 2010 Nov 1. PubMed PMID: 21041715.
99. Alibhai SM, Breunis H, Timilshina N, Marzouk S, Stewart D, Tannock I, Naglie G ,Tomlinson G, Fleshner N, **Krahn, M**, Warde P, Canning SD. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol. 2010 Dec 1;28(34):5030-7. Epub 2010 Nov 1.
100. van der Velde G, Pham B, Machado M, Ieraci L, Witteman W, Bombardier C, **Krahn M**. Cost-effectiveness of biologic response modifiers compared to disease modifying anti-rheumatic drugs for rheumatoid arthritis: A systematic review. Arthritis Care Res (Hoboken). 2011 Jan; 63(1):65-78.
101. Bhinder S, Chowdhury N, Granton J, **Krahn M**, Tullis E, Waddell T K, Singer LG. Feasibility of Internet-Based Health-Related Quality of Life Data Collection in a large patient cohort. Journal of Medical Internet Research 2010 Aug 19;12(3):e35.
102. Sander B, **Krahn M**, Bauch C, Fishman D, Fowler R, Kwong J, McGeer A, Maetzel A, Raboud J, Scales D, Gojovic M. Is a mass immunization program for pandemic (H1N1) 2009 good value for money? Evidence from the Canadian experience. Vaccine 2010 Aug 31; 28(38):6210-20. Epub 2010 Jul 17. PubMed PMID: 20643091.
103. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, Pham B, Ungar WJ, Einarson TR, Heathcote EJ, **Krahn M**. Tenofovir and Entecavir are the most effective antiviral agents for chronic hepatitits B: A systematic review and Bayesian meta-analyses. Gastroenterology, 2010 2010 Oct;139(4):1218-29. Epub 2010 Jun 20. Review. PubMed PMID: 20600036.
104. John-Baptiste A, **Krahn M**, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection drug use: meta-analysis and meta-regression. J Hepatol 2010 Aug;53(2):245-51. Epub 2010 May 11. PubMed PMID: 20537752.
105. Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G, Tu JV, Lee DS, goodman SG, Petrella R, O'Flaherty M, **Krahn M**, Capewell S. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. JAMA 2010 May 12;303(18):1841-7. PubMedPMID: 20460623.
106. Sander B, Kwong JC, Bauch CT, Maetzel A, McGeer A, Raboud JM, **Krahn M**. Economic appraisal of Ontario's Universal Influenza Immunization Program: a cost-utility anaylsis. PLoS Med 2010 Apr 6;7(4):e1000256. PubMed PMID: 20386727;PubMed Central PMCID: PMC2850382.
107. van der Velde G, Hogg-Johnson S, Bayoumi AM, Côté P, Llewellyn-Thomas H,Hurwitz EL, **Krahn M**. Neck Pain Patients' Preference Scores for Their Current Health. Quality of Life Research. 2010 Jun;19(5):687-700. Epub 2010 Mar 27. PubMed PMID:20349212; PubMed Central PMCID: PMC2874028.
108. Wilke DR, **Krahn M**, Tomlinson G, Bezjak A, Rutledge R, Warde P. Sex or survival: short-term versus long-term androgen deprivation in patients with locally advanced prostate cancer treated with radiotherapy. Cancer. 2010 Apr 15;116(8):1909-17. PubMed PMID: 20162716.
109. Klaassen RJ, **Krahn M**, Gaboury I, Hughes J, Anderson R, Grundy P, Ali SK, Jardine L, Abla O, Silva M, Barnard D, Cappelli M. Evaluating the ability to detect change of health-related quality of life in children with Hodgkin disease. Cancer. 2010 Mar 15;116(6):1608-14. PubMed PMID: 20143448.
110. Thein H, Wilson D, **Krahn M**, Hoare A, Dore G. Epidemiological and economic impact of potential increased hepatitis C treatment uptake in Australia. National Centre in HIV Epidemiology and Clinical Research; 2010:1-111.
111. **Krahn M**. "New" Evidence for Clinical Practice Guidelines. Patient 2010;3(2):1-7.
112. Machado M, Witteman W, Wijeysundera HC, Ieraci L, van der Velde G, Paulden M, **Krahn M**. Systematic Review of Economic Evaluations of Selected Cardiac Imaging Technoloiges in the Diagnosis of Coronary Artery Disease. Value in Health 2010;13(3):A163-4.
113. Alibhai SM, Breunis H, Timilshina N, Marzouk S, Stewart D, Tannock I, Naglie, G, Tomlinson G, Fleshner N, **Krahn M**, Warde P, Canning SD. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol. 2010 Dec 1;28(34):5030-7. Epub 2010

Nov 1. PubMed PMID: 21041708.

114. Thein HH, Gomes T, **Krahn M**, Wodchis WP. Health status utilities and the impact of pressure ulcers in long-term care residents in Ontario. Qual Life Res. 2010 Feb;19(1):81-9. Epub 2009 Dec 22. PubMed PMID: 20033300; PubMed Central PMCID: PMC2804787.
115. **Krahn M**, Bremner KE, Tomlinson G, Naglie G. Utility and health-related quality of life in prostate cancer patients 12 months after radical prostatectomy or radiation therapy. Prostate Cancer and Prostatic Diseases 2009; 12(4):361-8. Epub 2009 Sep 1. PubMed PMID: 19901935.
116. Panju A, Breunis H, Cheung A, Leach M, Fleshner N, Warde P, Duff-Canning S, **Krahn M**, Naglie G, Tannock I, Tomlinson G, Alibhai S. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. BJUI 2009 Mar;103(6):753-757
117. Mittmann N, Au H, Tu D, O'Callaghan C, Isogai P, Karapetis C, Zalcberg J, Evans W, Moore M, Siddiqui J, Findlay B, Colwell B, Simes J, Gibbs P, Links M, Tebbutt N, Jonker D, Working Group on Economic Analysis of National Canacer Institute of Canada Clinical Trials Group; Australasian Gastrointestinal Interest Group. J Natl Cancer Inst. 2009 Sep 2;101(17):1182-92. doi: 10.1093/jnci/djp232. Epub 2009 Aug 7. PubMed PMID: 19666851
118. **Krahn M.** Health technology Assessment in Canada: Problems and Opportunities. CJGIM May 2008;3(2):69-71
119. van der Velde G, Hogg-Johnson S, Bayoumi A, Cassidy JD, Côté P, Chan S, Subrata P, Hoving JL, Hurwitz, E. Bombardier C, **Krahn M**. Decision analysis of common non-invasive neck pain treatments. Medical Decision Making 2008 28:E1
120. Sander B, Bauch C, Fisman DN, Fowler R, Kwong JC, McGeer A, Zivkovic Gojovic M, **Krahn M**. Is a Mass Immunization Program for Pandemic (H1N1) 2009 Good Value for Money? Early Evidence from the Canadian Experience. PLoS Curr. 2009 Dec 17;1:RRN1137. PubMed PMID: 20043032; PubMed Central PMCID: PMC2795773.
121. Ku J, Alibhai S, Trachtenberg J, **Krahn M**, Nesbitt M, Kalnin R, Lockwood G. Changes in health utilities and health related quality of life over 12 months following radical prostatectomy. Canadian Urological Association Journal 2009 Dec;3(6):445-52. PubMed PMID: 20019969; PubMed Central PMCID: PMC2792418.
122. Gojovic MZ, Sander B, Fisman D, **Krahn M**, Bauch CT. Modelling mitigation strategies for pandemic (H1N1) 2009. CMAJ. 2009 Nov 10;181(10):673-80. Epub 2009 Oct 13. PubMed PMID: 19825923; PubMed Central PMCID: PMC2774362.
123. Chong CA, Li S, Nguyen GC, Sutton A, Levy MH, Butler T, **Krahn M**, Thein HH. Health-state utilities in a prisoner population: a cross-sectional survey. Health and Quality of Life Outcomes 2009 Aug 28;7:78. PubMed PMID: 19715571; PubMed Central PMCID: PMC2741437.
124. Waldmann A, Rohde V, Bremner K, **Krahn M**, Kuechler T, Katalinic A. Measuring prostate-specific quality of life in prostate cancer patients scheduled for radiotherapy or radical prostatectomy and reference men in Germany and Canada using the Patient Oriented Prostate Utility Scale-Psychometric (PORPUS-P). BMC Cancer. 2009 Aug 23;9:295.
125. **Krahn M**, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, Warde P, Naglie G. Healthcare costs associated with prostate cancer: estimates from a population-based study. BJU Int. 2010 Feb; 105 (3) : 338-46. Epub 2009 Jul 7. PubMed PMID: 19594734
126. John-Baptiste AA, Tomlinson G, Hsu PC, Krajden M, Heathcote EJ, Laporte A, Yoshida EM, Anderson FH, **Krahn M**. Sustained Responders Have Better Quality of Life and Productivity Compared With Treatment Failures Long After Antiviral Therapy for Hepatitis C. Am J Gastroenterol 2009 Oct;104(10):2439-48. Epub 2009 Jun 30. PubMed PMID: 19568230.
127. Thein HH, Yi Q, Heathcote EJ, **Krahn M.** Prognosis of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort. J Viral Hepat. 2009 Nov;16(11):802-13. Epub 2009 Apr 27. PubMed PMID: 19413692.
128. Chong CA, Chen IJ, Naglie G, **Krahn M**. How well do guidelines incorporate evidence on patient preferences? J Gen Intern Med. 2009 Aug;24(8):977-82. Epub 2009 Apr 23. Review.
129. Johnson AP, Sikich NJ, Evans G, Evans W, Giacomini M, Glendining M, **Krahn M**, Levin L, Oh P, Perera C. Health technology assessment: a comprehensive framework for evidence-based recommendations in Ontario. Int J Technol Assess Health Care. 2009 Apr;25(2):141-50. Review.

PubMed PMID: 19366496.

130. Alibhai SM, Mahmoud S, Hussain F, Naglie G, Tannock I, Tomlinson G, Fleshner N, **Krahn M**, Warde P, Klotz L, Breunis H, Leach M, Duff Canning S. Levels of sex hormones have limited effect on cognition in older men with or without prostate cancer. Critical Reviews in Onoclogy/Hematology 2010 Feb;73(2):167-75. Epub 2009 Apr 5. PubMed PMID: 19346137.
131. Kilbridge KL, Fraser G, **Krahn M**, Nelson EM, Conaway M, Bashore R, Wolf A, Barry MJ, Gong DA, Nease Jr RF, Connors AF. Lack of comprehension of common prostate cancer terms in an underserved population. Journal of Clinical Oncology. 2009 Apr 20;27(12):2015-21. Epub 2009 Mar 23.
132. van der Velde G, Hogg-Johnson S, Bayoumi AM, Cassidy JD, Côté P, Boyle E, Llewellyn-Thomas H, Chan S, Subrata P, Hoving JL, Hurwitz E, Bombardier C, **Krahn M**. Identifying the best treatment among common nonsurgical neck pain treatments: a decision analysis. J Manipulative Physiol Ther. 2009 Feb;32(2 Suppl):S209-18.
133. Hsu PC, Krajden M, Yoshida EM, Anderson FH, Tomlinson G, **Krahn M**. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? Liver Int. 2009 Mar;29(3):449-58.
134. John-Baptiste A, Varenbut M, Lingley M, Nedd-Roderique T, Teplin D, Tomlinson G, Daiter J, **Krahn M**. Treatment of hepatitis C infection for current or former substance abusers in a community setting. J Viral Hepat. 2009 Aug;16(8):557-67. Epub 2009 Feb 23.
135. Wan MJ, **Krahn M**, Ungar WJ, Caku E, Sung L, Medina LS, Doria AS. Acute appendicitis in young children: cost-effectiveness of US versus CT in diagnosis--a Markov decision analytic model. Radiology. 2009 Feb;250(2):378-86.
136. Panju AH, Breunis H, Cheung AM, Leach M, Fleshner N, Warde P, Duff-Canning S, **Krahn M**, Naglie G, Tannock I, Tomlinson G, Alibhai SM. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. BJU Int. 2009 Mar;103(6):753-7. Epub 2008 Oct 24.
137. Witteman H, Chignell M, **Krahn M**. A recommender system for prostate cancer websites. AMIA Annu Symp Proc. 2008 Nov 6:1177.
138. Thein HH, Yi Q, Dore GJ, **Krahn MD**. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy; a meta-analysis. AIDS 2008 Oct 1;22(15):1979-91. Review.
139. **Krahn M**, Naglie G. The next step in guideline development: Incorporating patient preferences. JAMA 2008 Jul 23;300(4):436-8.
140. Chen W, Wong T, Tomlinson G, **Krahn M**, Heathcote J. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. J Hepatol 2008 Nov;49(5):711-7. Epub 2008 Jun 6.
141. Sharieff W, Zlotkin SH, Ungar WJ, Feldman B, **Krahn M**, Tomlinson G. Economics of preventing premature mortality and impaired cognitive development in children through home-fortification: A health policy perspective. Int J Technol Assess Health Care 2008 Summer;24(3):303-11.
142. Thein HH, Yi Q, Dore GJ, **Krahn M**. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. Hepatology 2008 Aug;48(2):418-31. Review.
143. Naimark DM, Bott M, **Krahn M**. The half-cycle correction explained: Two alternative pedagogical approaches. 2008 Med Decis Making 2008 Sep-Oct;28(5):706-12.
144. Alibhai SM, Leach M, Tomlinson GA, **Krahn M**, Fleshner NE, Naglie G. Is there an optimal comorbidity index for prostate cancer? Cancer 2008 Mar 1;112(5):1043-50.
145. van der Velde G, Hogg-Johnson S, Bayoumi AM, Cassidy JD, Cote P, Boyle E, Llewellyn-Thomas H, Chan S, Subrata O, Hoving JL, Hurwitz E, Bombardier C, **Krahn M**. Identifying the best treatment among common nonsurgical neck pain treatments: a decision analysis. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S184-91
146. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JD, Côté P, **Krahn M**. Neck pain patients' evaluative scores for their current health. Medical Decision Making 2008 28:E1,
147. Cantor SB, Volk RJ, **Krahn M**, Cass AR, Gilani J, Weller SC, Spann SJ. Concordance of Couples' Prostate Cancer Screening Recommendations from a Decision Analysis. Patient. 2008 Jan 1;1(1):11-19.
148. Anonychuk AM, Tricco AC, Bauch CT, Pham B, Gilca V, Duval B, John-Baptiste A, Woo G, **Krahn M**.

Cost-effectiveness analyses of hepatitis A vaccine: a systematic review to explore the effect of methodological quality on the economic attractiveness of vaccination strategies. Pharmacoeconomics. 2008;26(1):17-32.Review.

149. Bauch CT, Anonychuk AM, Pham BZ, Gilca V, Duval B, **Krahn M**. Cost-utility of universal hepatitis A vaccination in Canada. Vaccine 2007 Dec 12;25(51):8536-48. Epub 2007 Oct 23.
150. You JJ, Woo A, Ko Dt, Cameron DA, Mihailovic A, **Krahn M**. Life expectancy gains and cost-effectiveness of implantable cardioverter/defibrillators for the primary prevention of sudden cardia death in patients with hypertrophic cardiomyopathy. Am Heart J. 2007 Nov;154(5):899-907.
151. Thein HH, Maruff P, **Krahn M**, Kaldor JM, Koorey DJ, Brew BJ, Dore GJ. Improved cognitive function as a consequence of hepatitis C virus treatment. HIV Medicine 2007 Nov;8(8):520-8.
152. Bremner KE, Tomlinson G, **Krahn M**. Marker states and a health state prompt provide modest improvements in the reliability and validity of the standard gamble and rating scale in prostate cancer patients. Qual Life Res. 2007 Dec;16(10):1665-75.
153. Bremner KE, Bayoumi AM, Sherman M, **Krahn M**. Management of solitary 1 cm to 2 cm liver nodules in patients with compensated cirrhosis: a decision analysis. Can J Gastroenterology. 2007 Aug;21(8):491-500. Review.
154. Bremner KE, Chong CA, Tomlinson G, Alibhai SMH, **Krahn M**. A review and meta-analysis of prostate cancer utilities. Medical Decision Making 2007 May-Jun;27:288-298
155. Thein HH, Maruff P, **Krahn M**, Kaldor JM, Koorey DJ, Brew BJ, Dore GJ. Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV) – monoinfected and HIV/HCV-coinfected individuals commencing HCV treatment. HIV Med 2007 Apr;8(3):192-202.
156. Bauch C.T., Rao A, Pham B, **Krahn M**, Gilca V, Duval B, Chen MH, Tricco AC. A dynamic model for assessing universal hepatitis A vaccination in Canada. Vaccine 2007 Feb 26;25:1719-1726. Epub 2006 Nov 27.
157. **Krahn M**, Bremner KE, Tomlinson G, Ritvo p, Irvine J, Naglie G. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. Qual Life Res. 2007 Apr;16(3):509-22.
158. Tricco AC, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, Anonychuk A, **Krahn M**, Moher D. A review of interventions triggered by hepatitis A infected food-handlers in Canada. BMC Health Serv Res. 2006 Dec 8;6:157.
159. Srinivasa Rao AS, Chen MH, Pham B, Tricco A, Gilca V, Duval B, **Krahn M**, Bauch C. Cohort effects in dynamic models and their impact on vaccination programmes: an example from hepatitis A. BMC Infectious Diseases 2006 Dec 5;6:174
160. Alibhai S, Leach M, **Krahn M**, Tomlinson G, Naglie G, Rethinking the 30-day mortality risk after radical prostatectomy,Urology 2006 Nov;68(5):1057-60
161. Chen W, **Krahn M**. Review: ribavirin is not better than placebo in chronic hepatitis C infection. ACP J Club 2006 Sept-Oct;145(2):47
162. Pinthus J, Witkos M, Fleshner N.E., Sweet J, Evans A, Jewett M.A., **Krahn M**, Alibhai S, Trachtenberg J. Prostate cancers scored as Gleason 6 in prostate biopsy are frequently Gleason 7 tumours at Radical prostatectomy: Implication on outcome. Journal of Urology 2006 Sept;176(3):979-84.
163. Thein HH, Butler T, **Krahn M**, Rawlinson W, Levy MH, Kaldor JM, Dore GJ. The effect of hepatitis C virus infection on health-related quality of life in prisoners. J Urban Health. 2006 Mar;83(2):275-88.
164. Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Black SE, Freedman M, Silbereld M, **Krahn M**. Utility-based quality of life measures in Alzheimer's disease. Qual Life Res. 2006 May;15(4):631-43
165. John-Baptiste A, **Krahn M,** Cook T, Straus S, Naglie G, Gray G, Tomlinson G. Decision Analysis in Aerospace Medicine: Costs and Benefits of a Hyperbaric Facility in Space. Aviation, Space & Environmental Medicine 2006 Apr;77:434-443.
166. Chong CA, Tomlinson G, Chodirker L, Figdor N, Uster M, Naglie G, **Krahn M**. An unadjusted NNT was a moderately good predictor of health benefit. J Clin Epidemiol 2006 Mar;59(3):224-33
167. Witkos M, Yi Q, Heathcote J, Kapral M, **Krahn M**. Predictors of antiviral therapy in a post-transfusion cohort of hepatitis C patients. Can J Gastro 2006 Feb;20(2):107-11
168. Hillmer M, **Krahn M**, Hillmer M, Pariser P, Naglie G. Prescribing patterns for Alzheimer disease: A survey of Canadian family physicians. Can Fam Physician 2006 Feb;52:208-209.

169. Roposch A, Wedge J, **Krahn M**. The role of the ossific nucleus in the treatment of established hip dislocation: A Treatment Decision Analysis. Clinical Orthopaedics and Related Research 2006 Aug;449:295-302.
170. Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Black S, Freedman M, Siberfeld M, **Krahn M**. Utility-based quality of life measures in Alzheimer's disease. Quality of Life Research May 2006;15(4):631-643
171. Wang ShX, Li YM, Sun BC, Zhang SW, Zhao WH, Wei MT, Chen KX, Zhao XL, Zhang ZL, **Krahn M**, Cheung AC, Wang PP. The SARS outbreak in a general hospital in Tianjin, China – the case of super-spreader. Epidemiol Infect. 2006 Aug;134(4):786-91.
172. Chen K, Wang P, Sun B, Yi Q, Perruccio A, Power D, Wang C, He M, Shibei Y, **Krahn M**, Cheung A, Hao X. Twenty-year secular changes in sex specific lung cancer incidence rates in an urban Chinese population. Lung Cancer 2006 Jan;51(1):13-9. Epub 2005 Nov 28.
173. Alibhai S, Leach M, Tomlinson G, **Krahn M**, Fleshner N, Holowaty E, Naglie G. 30 day mortality and major complications after radical prostatectomy: Influence of age and comorbidity. J Natl Cancer Inst. 2005 Oct 19;97(20):1525-32. Erratum in: J Natl Cancer Inst. 2007 Nov 7;99(21):1648.
174. Konski A, Sherman E, **Krahn M**, Bremner K, Beck JR, Watkins-Bruner D, Pilepich M. Economic analysis of a Phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86-10). Int J Radiat Oncol Biol Phys 2005 Nov 1;63(3):788-94
175. Cohen JH, Faughnan ME, Letarte M, Vandezande K, Kennedy SJ, **Krahn M**. Cost comparison of genetic and clinical screening in families with hereditary hemorrhagic telangiectasia. Am J Med Genet. 2005 Aug 30;137(2):153-160.
176. Ritvo P, Irvine J, Naglie G, Tomlinson G, Bezjak A, Matthew A, Trachtenberg J, **Krahn M**. Reliability and validity of the PORPUS, a combined psychometric and utility-based quality-of-life instrument for prostate cancer. J Clin Epidemiol. 2005 May;58(5):466-74.
177. Ritvo P, Wilson K, Willms D, Upshur R, Goldman A, Kelvin D, Rosenthal KL, Rinfret A, Kaul R, **Krahn M**; CANVAC Sociobehavioural Study Group. Vaccines in the public eye. Nat Med. 2005 Apr;11(4 Suppl):S20-4.
178. Thein HH, **Krahn M**, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. 2005 Mar;100(3):643-51.
179. **Krahn M**, John-Baptiste A, Yi Q, Doria A, Remis RS, Ritvo P, Friedman S. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. Vaccine. 2005 Feb 18;23(13):1549-58.
180. Benedikt F, Wayne J, **Krahn M**, Jurgen R. Differences and over-time changes in levels of prescription opioid analgesic dispensing from retail pharmacies in Canada, 2005-2010. J Pharmacoepidemiology and Drug Safety, [Epub July 13, 2011]
181. Kennedy ED, Urbach DR, **Krahn M**, Steinhart AH, Cohen Z, McLeod RS. Azathioprine or ileocolic resection for steroid-dependent terminal ileal Crohn's disease? A Markov analysis. Dis Colon Rectum. 2004 Dec;47(12):2120-30.
182. Alibhai SM, **Krahn M**, Fleshner NE, Cohen MM, Tomlinson GA, Naglie G. The association between patient age and prostate cancer stage and grade at diagnosis. BJU Int. 2004 Aug;94(3):303-6.
183. Volk RJ, Cantor SB, Cass AR, Spann SJ, Weller SC, **Krahn M**. Preferences of husbands and wives for outcomes of prostate cancer screening and treatment. J Gen Intern Med. 2004 Apr;19(4):339-48.
184. John-Baptiste A, Naglie G, Tomlinson G, Alibhai SM, Etchells E, Cheung A, Kapral M, Gold WL, Abrams H, Bacchus M, **Krahn M**. The effect of English language proficiency on length of stay and in-hospital mortality. J Gen Intern Med. 2004 Mar;19(3):221-8.
185. **Krahn M**, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making. 2004 Jan-Feb;24(1):20-9
186. Yi Q, Wang PP, **Krahn M**. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. J Viral Hepat. 2004 Mar;11(2):166-74.
187. Marras C, Lang A, **Krahn M**, Tomlinson G, Naglie G; Parkinson Study Group. Quality of life in early Parkinson's disease: impact of dyskinesias and motor fluctuations. Mov Disord. 2004 Jan;19(1):22-8

188. Alibhai SM, **Krahn M**, Cohen MM, Fleshner NE, Tomlinson GA, Naglie G. Is there age bias in the treatment of localized prostate carcinoma? Cancer. 2004 Jan 1;100(1):72-81.
189. Schwartz K, Alibhai S, **Krahn M**, Tomlinson G, Naglie G. Continued under-treatment of older men with localized prostate cancer. Journal of Urology 2003 Nov;62:860-865.
190. Ritvo P, Irvine J, Klar N, Wilson K, Brown L, Bremner KE, Rinfret A, Remis R, **Krahn M**. A Canadian national survey of attitudes and knowledge regarding preventive vaccines. J Immune Based Ther Vaccines. 2003 Nov 5;1(1):3.
191. **Krahn M**, Chapman KR. Economic issues in the use of office spirometry for lung health assessment. Can Respir J. 2003 Sep;10(6):320-6.
192. Alibhai SM. Naglie G. Nam R. Trachtenberg J. **Krahn M.** Do older men benefit from curative therapy of localized prostate cancer? J Clin Oncol. 2003 Sep 1;21(17):3318-27.
193. Nam RK. Jewett MA. **Krahn M**. Robinette MA. Tsihlias J. Toi A. Ho M. Evans A. Sweet J. Trachtenberg J. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. Can J Urol. 2003 Jun;10(3):1891-8.
194. Maetzel A, **Krahn M**, Naglie G. The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid arthritis. Arthritis Rheum. 2003 Jun 15;49(3):283-92.
195. Nordmann AJ, **Krahn M**, Logan AG, Naglie G, Detsky AS. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. Pharmacoeconomics. 2003;21(8):573-85.
196. Wang P, Yi Q, Scully L, Heathcote J, **Krahn M**. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. Can J Gastroenterol. 2003 Mar;17(3):183-6.
197. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, **Krahn M**. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. 2003 Mar;98(3):630-8.
198. **Krahn M**. Ritvo P. Irvine J. Tomlinson G. Bremner KE. Bezjak A. Trachtenberg J. Naglie G. Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. Medical Care. 2003 Jan;41(1):153-64.
199. Jassal SV, **Krahn M**, Naglie G, Zaltzman JS, Roscoe JM, Cole EH, Redelmeier DA. Kidney transplantation in the elderly: a decision analysis. J Am Soc Nephrol. 2003 Jan;14(1):187-96.
200. Taylor MC, Greig PD, Detsky AS, McLeod RS, Abdoh A, **Krahn M**. Factors associated with the high cost of liver transplantation in adults. Can J Surg. 2002 Dec;45(6):425-34.
201. **Krahn M**. Bremner KE. Asaria J. Alibhai SM. Nam R. Tomlinson G. Jewett MA. Warde P. Naglie G. The ten-year rule revisited: accuracy of clinicians' estimates of life expectancy in patients with localized prostate cancer. Urology 2002 Aug; 60(2):258-63,
202. Silberfeld M, Rueda S, **Krahn M**, Naglie G. Content validity for dementia of three generic preference based health related quality of life instruments. Qual Life Res. 2002 Feb;11(1):71-9.
203. Klaassen RJ, Doyle JJ, **Krahn M**, Blanchette VS, Naglie G. Initial bone marrow aspiration in childhood idiopathic thrombocytopenia: decision analysis. J Pediatr Hematol Oncol. 2001 Nov;23(8):511-8.
204. **Krahn M**. Ritvo P. Irvine J. Tomlinson G. Bezjak A. Trachtenberg J. Naglie G. Construction of the Patient-Oriented Prostate Utility Scale (PORPUS): a multiattribute health state classification system for prostate cancer. Journal of Clinical Epidemiology 2000 Sep;53(9):920-30.
205. Nam RK. Elhaji Y. **Krahn M**. Hakimi J. Ho M. Chu W. Sweet J. Trachtenberg J. Jewett MA. Narod SA. Significance of the CAG repeat polymorphism of the androgen receptor gene in prostate cancer progression. Journal of Urology 2000 Aug;164(2):567-72.
206. Mozurkewich EL, Naglie G, **Krahn M**, Hayashi RH. Predicting preterm birth: a cost-effectiveness analysis. Am J Obstet Gynecol 2000 Jun;182(6):1589-98.
207. Dowling AJ. Czaykowski PM. **Krahn M**. Moore MJ. Tannock IF. Prostate specific antigen response to mitoxantrone and prednisone in patients with refractory prostate cancer: prognostic factors and generalizability of a multicenter trial to clinical practice. Journal of Urology 2000 May 163(5):1481-5,
208. Naglie G, Tansey C, **Krahn M**, O'Rourke K, Detsky AS, Bolle H. Direct costs of coronary artery bypass grafting in patients aged 65 or more and those under 65. Canadian Medical Association Journal 1999 Mar 23;160(6):805-811.
209. Grover S, Zowall H, **Krahn M**. Prostate Cancer: 12. The economic burden. Canadian Medical

Association Journal 1999 Mar 9;160(5):685-90.
210. **Krahn M**, Coombs A, Levy I. Current and projected annual direct costs of screening asymptomatic men for prostate cancer using prostate specific antigen. Canadian Medical Association Journal 1999 Jan 12;160(1):49-57.
211. **Krahn M**, Guasparini R, Sherman M, Detsky AS. Costs and cost effectiveness of a universal, school-based, adolescent hepatitis B vaccination program. American Journal of Public Health. 1998 Nov;88(11):1638-1644.
212. Nam R, Jewett M, **Krahn M**. Prostate Cancer: 2. Natural history. Canadian Medical Association Journal 1998 Sep 22;159(6):685-91.
213. Bloomfield DJ, **Krahn M**, Neogi T, Panzarella T, Smith TJ, Warde P, Willan AR, Erst S, Moore MJ, Neville A, Tannock IF. Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic, hormone-resistant prostate cancer based on a Canadian Trial with palliative endpoints. Journal of Clinical Oncology 1998 Jun;16(6):2272-2279.
214. **Krahn M**, Naglie G, Naimark D, Redelmeier DA, Detsky AS. Primer on Medical Decision Analyis: Part 4 - Analyzing the Model and Interpreting the Results. Medical Decision Making 1997 Apr-Jun;17:142-151.
215. Naimark D, **Krahn M**, Naglie G, Redelmeier DA, Detsky AS. Primer on Medical Decision Analysis: Part 5 - Working with Markov Processes. Medical Decision Making 1997 Apr-Jun;17(2):152-159.
216. Redelmeier DA, Detsky AS, **Krahn M**, Naimark D, Naglie G,. Guidelines for Verbal Presentations of Medical Decision Analyses. Medical Decision Making 1997 Apr-Jun; 17(2):228-230.
217. Detsky AS, Naglie G, **Krahn M**, Naimark D, Redelmeier DA. Primer on Medical Decision Analysis: Part 1 - Getting Started. Medical Decision Making 1997 Apr-Jun;17:123-125.
218. Detsky AS, Naglie G, **Krahn M**, Redelmeier DA, Naimark D. Primer on medical Decision Analysis: Part 2 - Building a Tree. Medical Decision Making 1997 Apr-Jun;17:126-135.
219. Naglie G, **Krahn M**, Naimark D, Redelmeier DA, Detsky AS. Primer on Medical Decision Analysis: Part 3 - Estimating Probabilities and Utilities. Medical Decision Making 1997 Apr-Jun;17:136-141.
220. **Krahn M**, Berka C, Langlois P, Detsky A. Direct and indirect costs of asthma in Canada, 1990. Canadian Medical Association Journal 1996 Mar 15;154:821-831.
221. **Krahn M**, Naglie G. Principles of economic evaluation in cancer screening. Cancer Treat Res. 1996;86:25-40.
222. **Krahn M**, Mahoney J, Trachtenberg J, Eckman M, Pauker S, Detsky AS. Screening for prostate cancer: A decision analytic view. Journal of the American Medical Association 1994;272(10):773-780.
223. **Krahn M**, Detsky AS. Should Canada and the United States universally vaccinate infants against hepatitis B? A cost-effectiveness analysis. Med Decis Making. 1993 Jan-Mar;13(1):4-20.
224. **Krahn M**, Detsky AS. Universal hepatitis B vaccination: the economics of prevention. Canadian Medical Association Journal: 1992;146(1):19-20.
225. **Krahn M**, Naylor CD, Basinski AS, Detsky AS. Comparison of an aggressive (U.S.) and conservative (Canadian) policy for cholesterol screening and treatment. Annals of Internal Medicine 1991;115(4):248-55.
226. **Krahn,M**. Principles of Economic Evaluation in Surgery. World Journal of Surgery. 1999 Dec;23(12):1242-48.
227. Ritvo P, **Krahn M**, Magistretti A, Irvine J, Naglie G, Trachtenberg J. Comprehensively assessing the burden of prostate cancer. Canadian Journal of Urology 1996. 3:11-16.
228. **Krahn M**. Cost effectiveness analysis. Are the outputs worth the inputs? ACP J Club. 1996 May-Jun;124(3):82.
229. **Krahn M**. Trying to link recommendations to evidence. Abstracts of Clinical Care Guidelines. 1996 May;8(5):
230. **Krahn M**. Dying with or dying from prostate cancer: A decision-analytic view of the screening question. Chronic Diseases in Canada; 1995;Vol 16:S7-S11.
231. Ritvo P, **Krahn M**, Irvine J, Kraetschmer N, Trachtenberg J: The sociobehavioural side of prostate cancer treatment. Prostate Update 1995;1(4):4-5.
232. Detsky AS, Naglie IG, **Krahn M**. Clinical Decision Analysis. Annals of the Royal College of

Physicians and Surgeons of Canada 1994;27:157-159.

233. **Krahn M**. Cost effectiveness of asthma education. Chest 1994;106 (suppl. 4):264S-269S.
234. **Krahn M**. Issues in the cost-effectiveness of asthma education. Chest. 1994 Oct;106(4 Suppl):264S-269S. PubMed PMID: 7924554
235. Mahoney J, **Krahn M**. Decision Analysis for Localized Prostate Cancer. Canadian Journal of Continuing Medical Education 1994;6:45-60.
236. **Krahn M**, Detsky AS. Universal infant vaccination for hepatitis B in North America: A cost effectiveness analysis. Medical Decision Making 1993;13:4-20.
237. **Krahn M**, Gafni A. Discounting in the economic evaluation of health care interventions. Medical Care, May 1993;31(5); 403-18.

Reports

Xie XQ, Wang M, Schaink A, Krahn M. Pulmonary Rehabilitatio for Prostacute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Cost-Effectiveenss and Budget Impact Analysis. Health Quality Ontario. February 2015; pp. 1-47.

Five Most Significant Papers

1. **Krahn M**, Ritvo P, Naglie G, Irvine J, Bezjak A, Trachtenberg J. Construction of PORPUS: an Empirically Derived, Multi-attribute Health State Classification System for Prostate Cancer. Journal of Clinical Epidemiology.2000;53:920-930.

   A methodologically innovative approach to constructing a family of health status instruments based on a common health state classification system. This paper describes the construction of the classification system. This system has been used to develop i) a disease specific psychometric instrument; ii) a disease specific utility instrument, requiring direct preference elicitation; iii) a disease specific utility instrument that incorporates patient-derived weights, such that valid utilities can be generated by completing a 10 item questionnaire.

2. **Krahn M**, Mahoney J, Trachtenberg J, Eckman M, Pauker S, Detsky AS. Screening for Prostate Cancer: A Decision Analytic View. Journal of the American Medical Association 1994;272:773-780.

   Suggested that screening for prostate cancer may reduce health overall. Highly controversial, widely cited (>400 times), generated intense media attention, quoted and cited in numerous screening guidelines.

3. **Krahn M** et. al. Primer on medical decision analysis: Part 4 - Analyzing the model and interpreting the results. Medical Decisio Making 17.2 (1997):142-151

   Together with serveral collaborators we wrote a widely used 5 - part primer on how to conduct medical decision analysis. The primer has been used in many decision modeling courses, and has been cited over 800 times.

4. Thein HH et. al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta analaysis and meta regression. Hepatology 48.2 (2008): 418-431.
   This paper represents a world wide review of the literature of HCV prognosis, using a set of innovative methods. It is used in nearly all current HV pharmacoeconomic models . This and a companion paper on HCV prognosis in coinfected patients has been cited over 450 times.

5. **Krahn M**, Naglie G. The next step in guideline development: incorporating patient preferences. JAMA 300.4 (2008): 436-438.

   This editorial suggested a new direction in the development of clinical practice guikdelines, that involves

systematically incorporating patient preferences.

Non-Refereed Publications

1. Paulden M, Bergstrom N, Horn S, Rapp M, Barrett R, Watkiss M, Pham B, **Krahn M**. Turning for Ulcer Reduction (TURN) Study: Economic analysis. THETA Report TR 2013.2. (not available on web)
2. Rac V, Wong J, Brooker AS, Mitsakakis N, Pham B, Carcone S, **Krahn M**. Pressure ulcer multi-disciplinary Teams via Telemedicine (PUMTT): A pragmatic randomised controlled trial in long-term care - THETA Collaborative. THETA Report TR 2013.1. (not available on web)
3. Bergstrom N, Horn S, Pat M, Stern A, Barrett R, Watkiss M, **Krahn M**. Preventing Pressure Ulcers: A multi-site RCT in nursing homes. THETA Report TR 2012.1. June 2012
4. THETA Cardiac Group. Heart Failure (Multi-Disciplinary Community Care) Clinics field evaluation. THETA Report TR 2011.3
5. Brooker AS, Carcone S, Witteman W, **Krahn M**. Integrating quantitative preference-related evidence into HTA: The case of ventilation for COPD. THETA Report TR 2011.2. October 2011.
6. Trubiani G, Pham B, Stern A, Carcone S, Rosen L, **Krahn M**. Specialized multidisciplinary community-based care for chronic wounds: a field evaluation. THETA Report TR 2011.1. August 2011.
7. Wijeysundera H, Machado M, Farahti F, Wang X, Witteman W, van der Velde G, Tu J, Lee D, Goodman S, Petrella R, O'Flaherty M, **Krahn M,** Capewell S. Ontario IMPACT model. THETA Report TR 2010.1. January 2010
8. Relative cost-effectiveness of five non-invasive cardiac imaging Technologies for diagnosing coronary artery disease in Ontario - Toronto Health Economics and Technology Assessment Collaborative. THETA Report TR 2010.2. March 2010
9. Chen W, **Krahn M**. Cost-effectiveness of epidermal growth factor receptor gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. THETA Report TR 2010.3. November 2010.
10. Ieraci L, **Krahn M.** Cost-effectiveness of KRAS Genetic Testing for Anti-EGFR Therapy in metastatic colorectal cancer. THETA Report TR 2010.4. November 2010.
11. Paulden M, Franek J, Pham B, **Krahn M**. Cost-effectiveness of Oncotype-DX guided treatment in early breast cancer. THETA Report TR 2010.5. November 2010.
12. van der Velde G, Bombardier C, Ieraci L, **Krahn M**, Machado M, Pham B, Witteman W. Cost-effectivess of biologic response modifiers compared to disease modifying anti-rheumatic drugs for adults with rheumatoid arthritis: Systematic review of economic evaluations. THETA Report TR 2009.4. December 2009.
13. Pham B, Teague L, Mahoney J, Goodman L, Poss J, Li J, Sikich N, Lourenco R, Ieraci L, Witteman W, Carcone S, **Krahn M**. The cost-effectiveness of pressure-redistribution mattresses for early prevention of pressure ulcers in patients admitted to hospitals via the emergency department. THETA Report TR 2009.3. December 2009.
14. Wijeysunder H, Machado M, Wang X, van der Velde G, Sikich N, Witteman W, Tu J, Lee D, Goodman S, Petrella R, O'Flaherty M, Capewell S, **Krahn M**. Community-based care for the specialized management of heart failure: A cost-effectiveness and budget impact analysis. THETA Report TR 2009.2. November 2009.
15. **Krahn M,** Pham B, Stern A, John-Baptiste A, Bayoumi A, Carcone S, Chen W, Farahati F, Gomes T, Goodman L, Li J, Lourenco R, Machado M, Mahoney J, Poss J, Sander B, Sikich N, Teague L, Thein R, Wodchis W, Woo Gloria. Pressure Ulcer Prevention in Ontario Emergency Rooms Ontario Health Technology Advisory Committee, Toronto 2009.
16. **Krahn M,** Pham B, Stern A, John-Baptiste A, Bayoumi A, Carcone S, Chen W, Farahati F, Gomes T, Goodman L, Li J, Lourenco R, Machado M, Mahoney J, Poss J, Sander B, Sikich N, Teague L, Thein R, Wodchis W, Woo Gloria. Risk Assessment and Alternative Foam Mattresses to Prevent Pressure Ulcers in Long-Stay Clients of Ontario Community Care Access Centres Ontario Health Technology Advisory Committee, Toronto 2009
17. **Krahn M,** Pham B, Stern A, John-Baptiste A, Bayoumi A, Carcone S, Chen W, Farahati F, Gomes T,

Goodman L, Li J, Lourenco R, Machado M, Mahoney J, Poss J, Sander B, Sikich N, Teague L, Thein R, Wodchis W, Woo Gloria. The cost-effectiveness of prevention strategies for pressure ulcers in long-term care homes in Ontario Ontario Health Technology Advisory Committee, Toronto 2009.

18. **Krahn M,** Pham B, Stern A, John-Baptiste A, Bayoumi A, Carcone S, Chen W, Farahati F, Gomes T, Goodman L, Li J, Lourenco R, Machado M, Mahoney J, Poss J, Sander B, Sikich N, Teague L, Thein R, Wodchis W, Woo Gloria. Pressure Ulcer Prevention in Surgical Patients in Ontario Ontario Health Technology Advisory Committee, Toronto 2009.
19. **Krahn M**, van der Velde G, Ieraci L, Machado M, Paulden M, Witteman W. Cost-effectiveness of non-invasive cardiac imaging technologies compared to invasive coronary angiography in persons presenting with stable chest pain suspected of having coronary artery diseases: systematic review of economic evaluations.
20. **Krahn M**, Machao M, Farahati F, Ieraci L, Pham B, van der Velde G, Wijeysundera H, Witteman W, Tu J, Capewell S, Goodman S, Goeree R, Lee D, O'Flaherty M, Petrella R. The Ontario Cardiovascular Economic Model (OCVEM). Ontario Health Technology Advisory Committee, Toronto 2009.
21. **Krahn M**, Machao M, Farahati F, Ieraci L, Pham B, van der Velde G, Wijeysundera H, Witteman W, Tu J, Capewell S, Goodman S, Goeree R, Lee D, O'Flaherty M, Petrella R. A cost-effectiveness analysis was conducted by comparing the standard care cohort versus a hypothetical cohort of HF clinic patients. Ontario Health Technology Advisory Committee, Toronto 2009.
22. Pham B, Teague L, Mahone J, Goodman L, Stern A, Poss J, Li J, Sikich N, Lourenco R, Ieraci L, Witteman W, **Krahn M**. The cost-effectiveness of gel-filled overlays for the prevention of pressure ulcers in surgical patients. THETA Report TR 2009.1. November 2009.
23. **Krahn M**, William W, van der Velde G, Beyene J, Bombardier C, Ieraci L, Machado M, Pham B. Cost-effectiveness of Biologic Response Modifiers Compared to Disease Modifying Anti-Rheumatic Drugs for Adults with Rheumatoid Arthritis: Systematic Review of Economic Evaluations. Ontario Health Technology Advisory Committee, Toronto 2009.
24. Bayoumi A, John-Baptiste A, Chen M, Farahati F, **Krahn M**, Machado M, Sander B. The cost-effectiveness of prevention strategies for pressure ulcers in longterm care homes in Ontario: Projections of the Ontario Pressure Ulcer Model. THETA Report TR 2008.1. December 2008
25. **Krahn M**, McLachlin M, Rosen B, Sander B, Grootedorst P, Tomlinson G, John-Baptiste A, Frikemerid M. Hong Chen M, Woo G, Anonychuk A, Carcone S, Witteman H, Chen W, Liu K, Sampson M, Tricco A. Systematic review and cost-effectiveness analysis of screening for cervical cancer using liquid-based technology. [Technology overview number 40]. Ottawa: Canadian agency for Drugs and Technologies in Health; 2008.
26. Iowa prostate cancer consensus recommendation development committee (Konety B, **Krahn M**, Sharpe V, Albertson P, et. al.). Recommendations for screening and management of prostate cancer in men > 75 years of age. June 2005, Iowa Department of Public Health.
27. **Krahn M**, Yi Q, Wang P, Sherman M, Scully L, Heathcote EJ. Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986-1990. Second revision of prognostic model incorporating data from the compensation claimant cohort. Toronto: University of Toronto; 2005. 151 pp
28. Ontario Ministry of Health and Long Term Care (Smith T, Sherman M, **Krahn M** et. al.). Ontario's use of funding provided by the federal hepatitis C undertaking agreement. Ontario Ministry of Health, Nov 24, 2004. 35 pp
29. **Krahn M**, Wang P, Yi Q, Scully L, Heathcote EJ. Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986-1990 first revision of prognostic model incorporating data from the compensatn claimant cohort. Prognosis of Canadians infected with the hepatitis C virus. Toronto: University of Toronto; 2002 June 3. 133 pp.
30. **Krahn M**, Remis R, Hogg R, et al. Universal hepatitis A vaccination for adolescents and children in Canada: A cost effectiveness analysis. Toronto; Health Canada 2001.
31. **Krahn M**, Heathcote J, Scully L, Seeff L, Wong J. Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada between 1986 and 1990. Canadian Association for the Study of the Liver Working Group on Hepatitis C Prognosis. Report to Federal, Provincial, and Territorial Governments,

and Hepatitis C plaintiffs. March 1999.

32. **Krahn M**. Review. Plasma hepatitis B vaccine is safe and effective for health care workers. ACP Journal Club. March/ April 1998.
33. **Krahn M**, Sherman M, Hogg R, Remis R. Estimating the number of patients infected with HCV through the blood supply, 1986-1990. Report to Health Canada.
34. **Krahn M**. Review: Simvastatin therapy had favorable cost effectiveness ratios in lowering cholesterol levels in coronary heart disease. ACP Journal Club. July/August 1997.
35. **Krahn M**. Review: Simvastatin was cost effective in lowering cholesterol in coronary heart disease. ACP Journal Club, July-August 1997, p.21.
36. **Krahn M**. Review: costs of the 4S study. Evidence Based Medicine. November/December 1996, p.221.
37. **Krahn M**, Coombs A, Levy I. The impact of screening asympotmaticmen for prostate cancer using prostate specific antigen: background, current status, projected costs and health effects, and proposed governmental response. Report to the National Cancer Institute of Canada, March 1996
38. **Krahn M**. Book Review: Cost Effectiveness in Health and Medicine, Annals of the Royal College of Physicians and Surgeons, in press
39. **Krahn M.** Review: Simvastatin reduced the costs of coronary heart disease. Evidence Based Medicine, November/December 1996, p.221
40. **Krahn M**. Review: Multicenter Italian Pravastatin Trial. ACP Journal Club. (suppl.3):77, 1994.
41. **Krahn M.** Review: A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. ACP Journal Club, 118 (suppl 3): 93, 1993..
42. **Krahn M**, Gafni A. Discounting in the economic evaluation of health care interventions: from practice to theory to practice. McMaster Working Paper 92-2. Working paper series, Centre for Health Economics and Policy Analysis, May 1992.
43. **Krahn M**. Review: Alpha-Interferon for Chronic Hepatitis B: a Meta-analysis. ACP Journal Club.
44. **Krahn M** et al. The cost-effectiveness of prevention strategies for pressure ulcers in long-term care homes in Ontario: Projections of the Ontario Pressure Ulcer Model. THETA Report. December 2008
45. **Krahn M** et al. The cost-effectiveness of gel-filled overlays for the prevention of pressure ulcers in surgical patients. THETA Report. November 2009
46. **Krahn M** et al. Community-based care for the specialized management of heart failure: A cost-effectiveness and budget-impact analysis. THETA Report. November 2009
47. **Krahn M** et al. Cost-effectiveness of biologic response modifiers compared to disease modifying anti-rheumatic drugs for adults with rheumatoid arthritis: Systematic review of economic evaluations. THETA Report. December 2009
48. **Krahn M** et al. Cost-effectiveness of pressure-redistribution mattresses for early prevention of pressure ulcers in patients admitted to hospitals via emergency departments. THETA Report. December 2009

Book Chapters - Published or In Press

1. David Feeny, **Murray Krahn**, Lisa Prosser, and Joshua Salomon, "Identifying and Valuing Outcomes" Chapter for Panel II Edition, 2nd Panel on Cost-effectiveness in Health and Medicine. 2013 The University of California.
2. **Krahn M**, Neumann P, Prosser L. Cost Effectiveness Analysis as a Guide to Resource Allocation in Health: Roles and Limitations. Chapter for Panel II Edition, 2nd Panel on Cost-effectiveness in Health and Medicine 2013 The University of California.
3. Basu A, **Krahn M**, Kuntz K, meltzer D, Sculpher M. "Reflecting Uncertainty in Cost Effectiveness Analysis". Chapter for Panel II Edition, 2nd Panel on Cost-effectiveness in Health and Medicine 2013 The University of California.
4. **Krahn, Murray**, Karen E. Bremner, George Tomlinson, Paul Ritvo, Jane Irvine, and Gary Naglie, "Responsiveness of Disease-Specific and Generic Utility Instruments in Prostate Cancer Patients." Quality of Life Research , Vol. 16, No. 3, April, 2007, pp 509 - 522. [HUI2; HUI3; Construct Validity; Responsivene

5. Thein HH, YI Q, **Krahn M**. Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986-1990. Fourth Revision of Hepatitis C Prognostic Model Incorporating Data From the Compensation Claimant Cohort. April 2011.
6. **Krahn M**, John-Baptsite A. Common errors made in conducting decision analyses. Encyclopedia of Medical Decision Making, Kattan M (Ed.) Sage. 2009;
7. **Krahn M**, Sherman M, Hogg R, Remis R. Estimating the number of patients infected with HCV through the blood supply, 1986-1990. Report to Health Canada. 2007
8. **Krahn M**, Sherman M, Hogg R, Remis R, Zhou S, Wu J. Universal hepatitis A vaccination for adolescents and children in Canada: a cost-effectiveness and cost-utility analysis. Report to Health Canada.
9. **Krahn M**, Wang P, Yi Q, Scully L, Heathcote J. Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990: First Revision of Prognostic Model Incorporating Data From the Compensation Claimant Cohort. Report for the 1986-90 Compensation Claimants, Federal, Provincial, and Territorial Governments. 2000
10. **Krahn M,** Wang P, Yi Q, Scully L, Sherman M, Heathcote J. Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986-1990. Second Revision of HCV Prognostic Model Incorporating Data from the Compensation Claimant Cohort. Toronto: University Health Network, May 2005.
11. **Krahn M,** Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making 2004;24:20-29
12. **Krahn M**, Heathcote J, Scully L, Wang P, Yi Q. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990.
13. **Krahn M**, Heathcote J, Scully L, Seeff L, Wong J. Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada between 1986 and 1990. Canadian Association for the Study of the Liver Working Group on Hepatitis C Prognosis. Report to Federal, Provincial, and Territorial Governments, and Hepatitis C plaintiffs. March 1999.
14. Nam RK, Jewett MAS, **Krahn M**. Natural History. Chapter 2 in, Prostate Cancer: balancing the risks in diagnosis and treatment. The Clinical Basics Series. Canadian Medical Association 1999;9-20.
15. Grover, Steven A, Zowall Hanna, Coupal, **Krahn M**. The Economic Burden. Chapter 12, in Prostate Cancer: balancing the risks in diagnosis and treatment. The Clinical Basics Series. Canadian Medical Association 1999;143-154.
16. **Krahn M**. Review. Plasma hepatitis B vaccine is safe and effective for health care workers. ACP Journal Club. March/ April 1998.
17. **Krahn M**. Review: Simvastatin therapy had favorable cost effectiveness ratios in lowering cholesterol levels in coronary heart disease. ACP Journal Club 1997; 128: 45.
18. **Krahn M**. Review: Simvastatin was cost effective in lowering cholesterol in coronary heart disease. ACP Journal Club 1997; 127: 21.
19. **Krahn M**. Review: costs of the 4S study. Evidence Based Medicine 1996;1: 221.
20. **Krahn M**. Review: Simvastatin reduced the costs of coronary heart disease. Evidence Based Medicine 1996; 1: 221.
21. **Krahn M**, Levy I. Projected costs and health effects of PSA screening in Canada. Report to the National Cancer Institute of Canada, March 1996.
22. **Krahn M**, Naglie G. Principles of economic evaluation in screening programs. A. Miller ed Advances in Cancer Screening. Kluwer Academic Publishers, Boston 1996.
23. **Krahn M**, DiGuiseppi C. Hepatitis B Immunization in Childhood. Chapter 35 in The Canadian Guide to Clinical Preventive Health Care. The Canadian Task Force on the Periodic Health Examination. Ministry of Supply and Services Canada. Health Canada 1994; 397-403.
24. **Krahn M**. Review: Multicenter Italian Pravastatin Trial. ACP Journal Club. (suppl.3):77, 1994.
25. Maetzel A, **Krahn M**, Naglie G. Economic Evaluation of COX-2 NSAIDS in Canada. Technology Report, Canadian Coordinating Office for Health Technology Assessment (in press, peer reviewed)
26. **Krahn M**. Review: A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness

analysis. ACP Journal Club, 118 (suppl 3): 93, 1993.

27. **Krahn M**. Review: A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness strategies using cost-effectiveness analysis. ACP Journal Club 1993,118 (suppl 3):93.
28. **Krahn M**. Review: Alpha-Interferon for Chronic Hepatitis B: a Meta-analysis. ACP Journal Club.
29. **Krahn M**, Gafni A. Discounting in the economic evaluation of health care interventions: from practice to theory to practice. McMaster Working Paper 92-2. Working paper series, Centre for Health Economics and Policy Analysis, May 1992.

Commentary

1. **Krahn M,** Chen D. Ribavirin monotherapy for chronic hepatitis C infection: a Cochrane Hepato-Biliary Group systematic review and meta-analysis of randomized trials by Brok J, Gluud LL, Gluud C . A J Gastroenterol 2006;101:842-7

Abstracts Submitted

1. Dolovich L, Consiglio G, Abrahamyan L, Bojarski E, MacKeigan L, Pechlivanoglou P, Pojskic N, Rac V, Su J, **Krahn M**, Cadarette S. Ontario MedsCheck annual pharmacy medication review service: a comparison between initial and well established implementation periods. ICPE 2015 in Boston August 23-26, 2015.
2. Pechlivanoglou P, Abrahamyan L, MacKeigan L, Dolovich L, Consiglio G, Rac V, Shin J, Grootendorst P, Bojarski E, Cadarette S, **Krahn M**. Predictors of Ontario's Medication review program (MedsCheck Annual Service) Utilization Among Ontario Seniors. ICPE 2015 in Boston, Aug 23 - 26, 2015.
3. Hunger T, Schnell-Inderst P, Mayer A, Luzak A, Buhn S, Rochau U, Jahn B, Brixner D, Garrison L, **Krahn M,** Payne K, Clifford T, Steyerberg E, Lee Mortensen G, Dietz B, Pugner K, Hebborn A, Endel G, Siebert U. Results of an International Expert Task Force on a Health Technology Assessment Framework for Personalized Medicine in Cancer. HTAi 2015 in Oslo
4. Krahn M, Giacomini M, Miller F, Bayoumi A, Goeree R, Wagner F. Developing The Ontario Decision Framework (ODF): Basing decisions on clinical evidence, opportunity cost, and social values. HTAi 2015 in Oslo.
5. van der Velde G, Paulden M, Ieraci L, Wijeysundera H, Witteman W, **Krahn M**. Cost-effectiveness of Non-invasive Cardiac Imaging Technologies in Outpatients with Suspected Coronary Artery Disease. 33rd Annual Meeting of the Society of Medical Decision Making. *Medical Decision Making* 2012;32:E126-7.
6. van der Velde G, Paulden M, Ieraci L, Wijeysundera H, Witteman W, **Krahn M**. Cost-effectiveness of Non-invasive Cardiac Imaging Technologies in Outpatients with Suspected Coronary Artery Disease. 2012 CADTH (Canadian Agency for Drugs and Technologies in Health) Symposium 'Evidence Matters: Outcomes, Efficiency, Impact'. Conference Proceedings - Concurrent Oral Session B5 (Cardiovascular), page 39.
7. Bouchard M, **Krahn M** et al. Alleviating the injury burden by improving access to orthopaedic medical devices: A case stdy of Uganda. 2012 AAOS Annual Meeting.
8. Pham B, Tomlinson G, Grootendorst P, Witteman W, Wijeysundera H, **Krahn M**. A Systematic Approach to Calibration Analysis of Decision Models for Health Technology Assessment. 31st Annual Meeting of the Society for Medical Decision Making (SMDM), October 18, 2009 at Hollywood (Los Angeles), California, USA.
9. Wijeysundera H, Ko D, Tomlinson G, **Krahn M**. Medical Therapy versus Percutaneous Coronary Intervention in Symptomatic Coronary Artery Disease: Decision Analysis and Economic Evaluation . Canadian Cardiology Congress, October 26th 2009 at Edmonton, Canada
10. Wijeysundera HC, Machado M, Witteman W, Farahati F, van der Velde G, Tu J, Lee DS, Goodman S, Petrella R, O'Flaherty M, Capewell S, **Krahn M**. Reductions in coronary heart disease mortality associated with changes in risk factors in Ontario between 1994 and 2005. Submitted to The Canadian Cardiovascular

Congress - CCC, October 24 to 28, 2009 in Edmonton, AB

11. Chen W, Zagorski B, Krajden M, Heathcote J, **Krahn M**. Population-Derived Estimates of Direct Medical Costs Among Late-Stage Hepatitis C Patients with Diabetes Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium 2009, April 5, 2009, Ottawa, Canada
12. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Côté P, Cassidy D, **Krahn M.** Neck Pain Patients' Evaluative Scores for their Current Health. 29th Annual Conference SMDM October 22-24, 2007. Pittsburgh.
13. van der Velde G, Hogg-Johnson S, Bayoumi A, Cassidy D, Côté P, Boyle E, Llewellyn-Thomas H, Chan S, Subrata P, Hoving J, Hurwitz E, Bombardier C, **Krahn M.** Identifying the best treatment for non-specific neck pain: a decision analysis. 29th Annual Conference SMDM October 22-24, 2007. Pittsburgh.
14. Chen WD, **Krahn M**, Healthcote J. Prevalence and predictors of obesity among individuals testing positive for hepatitis C antibody in a multicultural, urban, tertiary care referral clinic. 58th Annual Meeting of the AASLD , Boston, Massachusetts November 2 - 6, 2007
15. Chen WD, **Krahn M**, Healthcote J. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. 58th Annual Meeting of the AASLD, Boston, Massachusetts November 2 - 6, 2007.
16. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JC, Côté P, **Krahn M**. Neck pain patients' evaluative scores for their current health. Palma International Forum IX Primary Care Research on Low Back Pain. October 4-6, 2007. Palma de Mallorca, Spain.
17. Kilbridge KL, Connors AF, Fraser G, Conaway M, **Krahn M**, Bashore R, Wolf A, Barry MJ. Barriers to measuring prostate cancer (CaP) quality of life (QOL) in underserved patients. Department of Defense Prostate Cancer Research Program Meeting, Innovative Minds in Prostate Cancer Today (IMPaCT), September 5-8, 2007, Atlanta, Georgia.
18. Thein H. H., Yi Q, Dore G, **Krahn M**. Natural history of hepatitis C virus infection in HIV-infected individuals in the era of HAART: systematic review and meta-analysis. IAS meeting March 2007.
19. Pham B, Escobar M, **Krahn M**, Tomlinson G, Thein R, Chen H. Multi-parameter evidence synthesis for disease prognosis in chronic hepatitis C virus infection. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
20. Bauch C, Anonychuk A, Pham B, Gilca V, Duval B, **Krahn M**. Cost-effectiveness of universal hepatitis A vaccination in Canada via dynaic modeling. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
21. Anonychuk A, **Krahn M**, Gilca V, Pham B, Duval B, Bauch C. The cost of hepatitis A in Canada: Ministry of societal perspectives. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
22. Chong AKY, Chen I, Naglie G, **Krahn M**. Clinical practice guidelines incorporate evidence on patient preferences? 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006.
23. John-Baptiste A, **Krahn M**, Tomlinson G. Natural history of chronic HCV infection obtained through injection drug use: A Bayesian meta-analysis. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
24. Chen WD, Cope S, Watkins J, Heathcote J, **Krahn M**. Primary prevention of esophageal variceal bleeding among cirrhotic patients with hepatitis c and grade 2 to 3 esophageal varices: a cost-utility analysis. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
25. Bremner KE, Trachtenberg J, **Krahn M**. The effects of age, clinical stage, and treatment history on disease specific utility in prostate cancer patients. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
26. Varenbut M, John-Baptiste A, Teplin D, Lingley M, Daiter J, **Krahn M**. Treatment of hepatitis C infection

in patients on methadone maintenance in a community setting. CSAM 2006 Conference.

27. Tricco A, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, **Krahn M**, Moher, D. Burden of hepatitis A intervention triggered by infected food-handlers in Canada. CNIC 2006 Conference
28. Thein HH, Butler T, **Krahn M**, Rawlinson W, Levy M, Kaldor JM, Dore GJ. The effect of hepatitis C virus infection on health-related quality of life in prisoners. 2nd Annual Canadian Association for the Study of the Liver Winter Meeting 2006, Toronto, Canada.
29. Witkos M, Bremner KE, Trachtenberg J, **Krahn M**. The effects of age, clinical stage, and treatment history on disease specific utility in prostate cancer patients. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006
30. G. va der Velde, M. **Krahn, S**. Hogg-Johnson, E. Hurwitz, H. Llewellyn-Thoms, J.D. Cassidy, P. Cote. Neck pain patients' preferences for health outcomes associated with neck pain. Palma International Forum IX Primary Care Research on Low Back Pain. October 4-6, 2007 Palma de Mallorca, Spain.
31. **Krahn M**. Effect of age on preferences for health outcomes in prostate cancer. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007.
32. **Krahn M**. The patient-oriented prostate utility scale (PORPUS-U_i) – a prostate cancer-specific utility instrument. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007.
33. **Krahn M**. Predictors of life-time and stage-specific costs of prostate cancer. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007.
34. **Krahn M**, Zagorski B, Forde N, Laporte A, Alibhai S, Bremner KE, Tomlinson G, Naglie G. Predictors of stage-specific and lifetime coss of prostate cancer. 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006.

Abstracts Accepted for Oral or Poster

1. **Krahn M**, Miller F, Bayoumi A, Giacomini M, Goeree R, Wagner F, Winsor S, Schunemann H, van de Velde G, Pham B, Petersen S, Brooker AS, Rac V. Improving the appraisal of non-drug technologies: Revising the Ontario Decision Framework. 2015 CADTH Symposium Apr 12 -14, TCU Place in Saskatoon, SK. [accepted for panel session]
2. Rac V, Abrahamyan L, **Krahn M**. Complex interventions for comparative effectiveness and health technology assessment. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for 1/2 day workshop)
3. **Krahn M**, Wong W. Public policy in the post-interferon era: Can we afford to cure Hepatitis C? 2015 CADTH Syposium April 12 - 14, TCU Place in Saskatoon, SK [accepted for panel sessions].
4. Wong W, Feld J, **Krahn M**. Cost-effectiveness of a one-time national hepatitis C screening program: impact of a selective drug reimbursement policy. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted oral presentation)
5. Miller F, Barg C, **Krahn M**, Lehoux P, Peacock S, Rac V. Two solitudes: HTA and procurement as pathways to the adoption of health technologies. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for oral presentation)
6. Rac V, Wong J, Mitsakakis N, Haratsidis E, **Krahn M**. Implementation challenges of a community-based pragmatic randomized controlled trial in wound care. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
7. Mitsakakis N, Bremner K, **Krahn M**. Benefits of transformations in mapping health utilities. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
8. Pechlivanoglou P, Abrahamyan L, Pham B, Hsu S, Paulden M, **Krahn M**. Projecting mortality rates in economic evaluation: A simulation study. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
9. Pham B, Fowler R, Tanuseputro P, Manuel D, Sikich N, Baidoobonso S, Pechlivanoglou P, Levin L, Guerriere D, Coyte P, **Krahn M**. Including the patient's family in cost-effectiveness analysis of end-of-life

interventions. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)

10. Xie X, Wang M, Schaink A, **Krahn M**. Pulmonary rehabilitation for post-acute exacerbations of chronic obstructive pulmonary disease: A cost-effectiveness and budget impact analysis. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
11. Tadrous M, mamdani MM, Juurlink DN, **Krahn M**, Levesque LE, Cadarette SM. Looking both ways before using the Disease Risk Score (DRS): Performance of the DRS in a cohort with known selection bias. International Conference in Pharmacoepidemiology and Therapeutic Risk Management Annual Meeting. October 2014, Taipei, Taiwan [poster presentation]
12. Rac V, Abrahamyan L, **Krahn M**. Complex interventions for comparative effectiveness and health technology assessment. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. (1/2 day short course teaching)
13. Pechlivanoglou P, Abrahamyan L, Pham B, Paulden M, **Krahn M**. The impact of estimating mortality rates in cost-effectiveness analysis: A simulation study. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [oral presentation]
14. Pham B, Fowler R, Tanuseputro P, Manuel D, Sikich N, Baidoobonso S, Pechlivanoglou P, Levin L, **Krahn M**. Cost-effectiveness analysis of palliative team care for patients nearing end-of-life. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [oral presentation]
15. Muhlberger N, Heijnsdijk E, Kurzthaler C, **Krahn M**, Oberaigner W, Klocker H, Conrads-Frank A, Sroczynski G, Siebert U. The oncotyrol prostate cancer outcome and policy model-lessons learned from natural history calibration. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[oral presentation]
16. Wong W, Feld J, Wong T, **Krahn M**. Cost-effectiveness of screening hepatitis C in Canada. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
17. Wong W, Hicks L, Tu HA, **Krahn M**, Pritchard K, Feld J, Chan K. Cost-effectiveness of hepatitis B virus screening before adjuvant chemotherapy in patients with early stage breast cancer. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
18. Nanwa N, Kendzerska T, **Krahn M**,. Kwong J, Daneman N, Witmann W, Mittmann N, Cadarett S, Rosella L, Sander B. The economic impact of clostridium difficile: A systematic review. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
19. Rac V, Wong J, Mitsakakis N, Pechlivanoglou P, Carcone S, **Krahn M**. Wound Interdisciplinary Teams (WIT): A community-based pragmatic randomized controlled trial. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
20. Wong J, Rac V, Mitsakakis N, Haratsidis E, **Krahn M**. Implementation challenges of a community-based pragmatic randomized controlled trial in wound care. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. (poster presentation)
21. Nanwa N, Kwong J, **Krahn M**, Daneman N, Lu H, Govindarajan A, Rosella L, Cadarette S, Sander B. Adopting the phase-of-care approach to estimate costs of a secondary diagnosis of clostridium difficile. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
22. Jiang M, Pechlivanoglou P, Wong J, Mitsakakis N, Carcone S, Pham B, Rac V, **Krahn M**. Cost-effectiveness analysis of systmatic referral to multidisciplinary wound care teams in Ontario. Evidence from teh wound interdisciplinary teams (WIT) trial. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
23. Tawfik A, Wodchis W, Hoch J, **Krahn M**. Estimating healthcare costs for decision-analytic models in atrial fibrillation using administrative data. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
24. Tadrous M, Mamdani MM, Juurlink DN, **Krahn M**, Levesque LE, Cadarette SM. Looking both ways before using the Disease Risk Score (DRS): Performance of the DRS in a cohort with known selection bias.

Canadian Association of population Therapeutics Annual Conference. November 2014, Toronto ON, Canada [poster presentation].

25. Tu HA, Deeks S, Morris S, Strifler L, Crowcroft N, Jamieson F, Kwong J, Coyte P, **Krahn M**, Sander B. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for poster presentation).
26. Boehme K, Perlis N, Finelli A, Alibhai S, Kulkarni G, **Krahn M**, Bremner K. Developing the Bladder Utility Symptom Scale (BUSS): A multiattribute health state classification system for bladder cancer. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for poster presentation).
27. Wijeysundera H, Wang X, Bennell M, Ko D, Abrahamyan L, Tu J, Austin P, **Krahn M**. Characteristics of multi-disciplinary heart failure clinics that predict 1-year cumulative health care costs; a population-based study. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for oral presentation).
28. Wong W, Tu HA, Chen W, Feld J, Chelak K, Lee K, **Krahn M**. The hepatitis C drug pipeline: collaboration between academic and HTA agency partners to develop an early economc model. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for oral presentation).
29. Hogan ME, Shah V, Katz J, **Krahn M**, Taddio A. A systematic review of cost-of-illness studies of chronic pain in children. 9th International Symposium on Pediatric Pain. Stockholm, Sweden. June 17-20, 2013. (accepted for poster presentation).
30. Hogan ME, Shah V, Katz J, **Krahn M**, Taddio A. A systematic review of cost-of-illness studies for chronic pain. Canadian Association for Health Services and Policy Research Annual Conference, Vancouver, British Columbia. May 28-30, 2013. (accepted for oral presentation).
31. **Krahn M.** Economic evaluation of mono and sequential hormone therapies for ER+ women with early breast cancer in Canada. ISPOR 15th Annual European Congress, November 3-7, 2012, Berlin, Germany. (accepted for poster presentation).
32. **Krahn M**. Lessons learned from a cross-validaton between a discrete-event simulation model and a Markov Model for personalized breast cancer treatment. ISPOR 15th Annual European Congress November 3-7, 2012, Berlin, Germany. (accepted for podium presentation).
33. Sander B, Ormanidhi O, Paszat L, Atkin K, Murphy J, **Krahn M**, Deeks S. The cost-effectiveness of integrated cervical cancer prevention strategies in the Ontario setting - can we do better? The 34th annual meeting of the Society for Medical Decision Making, Phoenix AZ. October 17 - 20, 2012 (Oral presentation).
34. Tawfik A, Wodchis W, Hoch J, **Krahn M**. Cost-effectiveness of stroke prevention therapies in atrial fibrillation patients: A new generation of drugs. The 34th annual meeting of the Society for Medical Decision Making, Phoenix AZ. October 17 - 20, 2012 (Poster presentation)
35. Karen E. Bremner, **Murray D. Krahn**, K. Robin Yabroff, Jeffrey S. Hoch, Lisa Barbera, Ning Liu, Michael J. Barrett, Joan L. Warren. Opportunities and challenges in using administrative data for cross-country comparisons of health care costs. 34th Annual Meeting of the Society for Medical Decision Making, October 17-20, 2012 in Phoenix, Arizona, USA. (poster presentation).
36. **M.D. Krahn**, K.E. Bremner, J. Luo, S.M.H. Alibhai. UsingAdministrative Databases to Estimate Health Care Costs from Adverse Drug Effects: The Case of Prostate Cancer. Biennial Society for Medical Decision Making European Meeting. June 10 - 12, 2012. Institute of Health Management and Health Economics, University of Oslo, Oslo, Norway (oral presentation).
37. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M**. Evaluation of Trends in the Cost of Initial Cancer Treatment in Ontario. Canadian Association of Health Services and Policy Research, Montreal Quebec. May 29-31,2012 (poster)
38. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M**. First-year Costs of Cancer Care in Ontario. Canadian Centre for Applied Research in Cancer Control Conference, May 28, 2012. Montreal Quebec.
39. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M**. Using Administrative Health Care Data to Inform Cancer Care Research and Policy: Estimating the Economic Burden of Disease. Ontario Institute for Cancer Research/Cancer Care Ontario 4th Annual Meeting, May 17, 2012. Toronto. (poster)

40. Wijeysunder H, Mitsakakis N, **Krahn M**, Trubiani G, Ko D, Austin P, Lee D, Wang X. A population-based study to evaluate the effectiveness of multi-disciplinary heart failure clinics and identify important service components. American Heart Association Quality of Care and Outcomes Research 2012 Scientific Sessions May 9 – 11, 2012, Atlanta, GA. (accepted for poster presentation).
41. **M.D. Krahn**, K.E. Bremner, J. Luo, S.M.H. Alibhai. Using Ontario Administrative Data to Estimate Health Care Costs of Drug Adverse Effects: The Case of Prostate Cancer. Fourth Annual Meeting of the Ontario Institute for Cancer Research/ Cancer Care Ontario Health Services Research Program. May 17, 2012 at the Faculty Club, University if Toronto (poster presentation).
42. Wong W, Bayoumi A, **Krahn M**, Thein HH. Developing a complex agent network model to predict HIV and HCV incidence in Canada. The 3rd International Conference on Infectious Disease Dynamics, Boston, MA, USA 2011 (accepted for poster presentation)
43. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. American Association for the Study of Liver Disease (AASLD), October 29-November 2, 2011, Boston, MA (accepted for poster presentation)
44. Brooker AS, Carcone S, **Krahn M**. Integrating quantitative preference-related evidence into health technology assessment: The case of ventilation for chronic obstrructive pulmonary disease. The 33rd annual meeting of the Society for Medical Decision Making. Chicago IL. October 22- 26, 2011. (accepted for poster presentation)
45. **Krahn M**. Predicting utility scores for prostate cancer: mapping the prostate cancer index to the patient oriented prostate utility scale (PORPUS). The 33rd annual meeting of the Society for Medical Decision Making. Chicago IL. October 22- 26, 2011. (Accepted for oral presentation)
46. **Krahn M**, Bremner K, Zagorski B, Alighai S, Tomlinson G, Naglie G. Using large administrative datasets and chart reviews to estimate costs for health states: the case of prostate cancer. 33rd annual meeting of the Society for Medical Decision Making. Chicago IL. October 22- 26, 2011. (Accepted for oral presentation)
47. Wong W, Bayoumi A, **Krahn M**, Thein HH. Developing a complex agent network model to predict HIV and HCV incidence in Canada. The 33rd Annual Meeting of the Society for Medical Decision Making, Chicago, IL 2011 (accepted for oral presentation)
48. Paulden m, Franek J, Pham B, **Krahn M**. Gene expression profiling for guiding adjuvant chemotherapy decisons in women iwth early breast cancer: A cost-effectiveness analysis of 1000 strategies for the provision of adjuvant! Online, 21-Gene assay and chemotherapy. The 33rd Annual Meeting of the Society for Medical Decision Making, Chicago, IL 2011 (accepted for oral presentation)
49. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Disease Burden of Chronic Hepatitis B among Immigrants in Canada. The 33rd Annual Meeting of the Society for Medical Decision Making, October 22-26, 2011, Chicago IL (accepted for poster presentation)
50. Hincapie CA, Schieir O, Cote P, Hogg-Johnson S, Paulden M, **Krahn M**, van der Velde G. A cost-effectiveness analysis of common nonsurgical treatments for neck pain. National Student Conference of the Canadian Society of Epidemiology and Biostatistics, June 19-20, 2011, Montreal Canada (Accepted for oral presentation)
51. Lee L, Hodgson D, Crump M, Khor S, Luo J, **Krahn M**, Bremner K, Hoch J. Impact of Rituximab on Outcomes of Very Elderly Patients With Diffuse Large B-Cell Lymphoma. 11th International Conference on Malignant Lymphoma, Lugano Switzerland, June 15-18, 2011 (Accepted for poster presentation)
52. van der Velde G, Schieir O, Hincapié C, Coté P, Hogg-Johnson S, Paulden M, **Krahn M**. Economic Evaluation of the Most Commonly Used Non-surgical Treatments for Neck Pain in Canada: A Cost-utility Analysis. International Health Economics Association (iHEA) 8th World Congress, July 10-13, 2011, Toronto, Canada. (Accepted for oral and poster presentation)
53. van der Velde G, Hincapié C, Schieir O, Coté P, Hogg-Johnson S, Paulden M, **Krahn M**. Cost-effectiveness of the Most Common Nonsurgical Treatments for Neck Pain. 16th International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Poster Session II, May 24, 2011, Baltimore, United States. (Accepted for poster presentation - February 23, 2011)
54. Chen W, Ellis P, **Krahn M**. Cost-effectiveness of epidermal growth factor receptor gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario, Canada. The 33rd Annual Meeting of the Society for Medical Decision Making, October 22-26, 2011, Chicago IL (accepted for oral

presentation)

55. Ieraci L, **Krahn M**, Paulden M, van der Velde G, Wijeysundera H, Machado M, Witteman W. The cost – effectiveness analysis of five non-invasive cardiac imaging technologies in Ontario. 32nd Annual Meeting of Society for Medical Decision Making Oct 24-27, 2010, Sheraton Centre Toronto, Ontario Canada (Accepted for poster presentation).
56. Bornstein M, Franek J, Parthimos M, Nakhai-Pour H, Ieraci L, Paulden M, **Krahn M**, Onetto N, Levin L. Pharmacogenetic testing and evidence-based decision-making in Ontario: The application of Ontario's decision determinants framework to the evaluation of pharmacogenetic tests. 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (Accepted for poster presentation.
57. de oliveira C, Wijeysundera H, Tobe S, Moy Lum-Kwong M, Sychowski S, Tu J, **Krahn M**. An economic analysis of heart and stroke foundation of Ontario's Hypertension Management Initiative (HMI). 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (Accepted for oral presentation.
58. Tsui T, Boon H, **Krahn M**, Boecker A, Kachan N. Using the means-end chain approach to map consumer decsion making: The case of natural health products. 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (Accepted for oral presentation).
59. Lee L, Khor S, Crump M, Hoch J, Bremner K, **Krahn M**, Hodgson D. "Challenges in the Identification of Accurate Pathological Diagnoses and Treatment for B-cell Lymphoma: A Comparison of Ontario Databases", presented at Cancer Care Ontario Research Day, Toronto, Ontario, April 2010. (accepted for poster presentation)
60. Beate S, Bauch C, Fisman D, Fowler R, Kwong J, McGeer A, **Krahn M**. Is a mass immunization program for pandemic (H1N1) 2009 good value for money? Early evidence from the Canadian experience. 14th International Congress on Infectious Disease, Miami FL, March 9-12, 2010(Accepted for oral presentation)
61. Thein HH, **Krahn M**, Hoare A, Dore G, Wilson D. The current and future burden of hepatitis C in Australia. 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (Accepted for oral presentation).
62. Sikich N, Pham B, **Krahn M**, Levin L. A systmatic review and meta-analysis of survival curve data to determine the effectiveness of liver and kidney transplantation in persons with end-stage organ failure and human immunodefieciency virus. 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (Accepted for oral presentation).
63. Zivkovic Gojovic M, Bauch C, Fishman D, **Krahn M**, Sander B. Assessing H1N1(2009) mitigation strategies under epidemiologic and programmatic uncertainty. 14th International Congress on Infectious Diseases, Miami FL, March 9-12, 2010.(poster presentation).
64. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. The 32nd Annual Meeting of the Society For Medical Decision Making, October 24-27, 2010, Toronto, Ontario Canada (accepted for poster presentation).
65. Pham B, Tomlinson G, Grootendorst P, **Krahn M**. Monte Carlo approach to calibration of disease history models for health technology assessment: A case study. The 32nd Annual Meeting of the Society For Medical Decision Making, October 24-27, 2010, Toronto, Ontario Canada (accepted for poster presentation).
66. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium, April 18-20, 2010 Halifax, NS, Canada (accepted for poster presentation)
67. Sander B, **Krahn M**, Bauch C, Fisman D. Impact of mathematical modelling on health policy decision-making in the context of the recent novel Swine-Origin Influenza A Virus (SOIV) outbreak response in Ontario, Canada. 31st Annual Meeting of the Society for Medical Decision Making (SMDM) October 18-21, 2009, California, USA (Accepted for poster presentation)
68. Lathia N, Walker S, Cheung M, **Krahn M**, DeAngelis C, Mittmann N. Cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in lymphoma patients receiving r-chop chemotherapy. 2009 Annual Meeting of the American Society of Hematology in New Orleans, LA,

(Accepted for poster presentation)

69. van der Velde G, **Krahn M**, Machado M, Ieraci L, Witteman W, Pham Ba'. The cost-effectiveness of biologic disease modifying anti-rheumatic drugs (DMARDS) compared to conventional DMARDS: A systematic review of economic evaluations. 31st Annual Meeting of the Society for Medical Decision Making (SMDM) Oct 18-21, 2009, California, USA (Accepted for poster presentation)
70. **Krahn M**. Collaboration between HTA agency and health authority: Ontario Canada. 6th Annual meeting HTAi Globalisation and Health Technology Assessment. Singapore June 21-24, 2009 (accepted for panel session)
71. **Krahn M**. Economic evaluation of preventive strategies for pressure ulcers. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
72. Thein HH, **Krahn M** et. al. Health status utilities in long-term care residents in Ontario. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
73. Chen WD, **Krahn M** et al. Economic evaluation of pressure ulcer preventive strategies for long-term residents in Ontario. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
74. Chen WD, **Krahn M** et al. Economic evalutation of preventive strategies for pressure ulcers: A systematic review. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
75. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of Ontario's universal influenza immunization program. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (accepted for oral presentation).
76. Woo G, Tomlinson G, Pham B, **Krahn M**. Comparing efficacies of treatments for chronic hepatitis B: A Bayesian mixed treatment comparison meta-analysis. . iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (accepted for poster presentation)
77. Mittmann N, Evans B, Leighl N, Rocchi A, **Krahn M**, Peacock S, Taylor S, Au HJ, Oh p, Jacobs P, Reynard P, Husereau D, Isogai P, Longo C, Marshall D, Coyle D, Meyer R, Kee P. Economic guidelines for oncology products: Adaptation of the Canadian Agency for Drugs and Technologies in Health (CADTH) technology assessment guidance document. ASCO 2009
78. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of Ontario's universal influenza immunization program. International Health Economics Association 7th World Congress 2009.
79. Woo G, Pham B, Tomlinson G, **Krahn M**. Comparing efficacies of treatements for chronic hepatitis B: A Bayesian mixed treatment comparison meta-analysis. iHEA 7th World Congress on Health Economics July 12-15, 2009. Beijing, China (Accepted for Poster presentation)
80. Machado M, Wijesundera H, Farahati F, Witteman W, van der Velde G, Ieraci, L, Pham B', **Krahn M**. Development of the Ontario Cardiovascular Economic Model. Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium 2009, April 5, 2009, Ottawa, Canada (Accepted for Poster presentation)
81. Woo G, Pham B, Tomlinson G, **Krahn M**. Comparing efficacies of treatements for chronic hepatitis B: A Bayesian mixed treatment comparison meta-analysis. 44th Annual Meeting of the European Association for the Study of the Liver (EASL), April 22-26, 2009, Copenhagen, Denmark (Accepted for Poster presentation)
82. Chen W, **Krahn M**, et. Al. Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. iHEA 7th World Congress on Health Economics July 12-15, 2009. Beijing, China (Accepted for Oral presentation)
83. Machado M, Pham B, Chen W, Stern A, **Krahn M**. Budget and health impact of strategies for preventing pressure ulcers in long-term care facialities in Ontario. 30th Annual Conference SMDM October 18-22, 2008. Philadelphia, Pennsylvania. [Accepted for Poster presentation]
84. Sander B, Kwong J, Bauch CT, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of

Ontario's Universal Influenza Immunization Program. 30th Annual Conference SMDM October 18-22, 2008. Philadelphia, Pennsylvania. [Accepted for an oral presentation].

85. Thein HH, Pham B, **Krahn M**, Wodchis W. Health status utilities in long-term care residents in Ontario. The 30th Annual Meeting of the Society for Medical Decision Making. October 18 - 22, 2008, Philadelphia, Pennsylvania. [Poster]

Abstract Published

1. Goldhar H, Yan A, Ko D, Earle C, Tomlinson G, Trudeau M, **Krahn M**, Krzyzanowska M, Pal R, Brezden C, Gavura S, Lien K, Chan K. Long-term risk of heart failure associated with adjuvant trastuzumab in breast cancer patients. 2014 ASCO Annual Meeting (May 30 - June 3, 2014)
2. Chan M, Yan A, Ko D, Earle C, Tomlinson G, Trudeau M, **Krahn M**, Krzyzanowska M, Pal R, Brezden C, Gavura S, Lien K, Chan K. Long-term cardiovascular (CVS) and survival outcomes with early discontinuation of adjuvant trastuzumab (T) for breast cancer. 2014 ASCO Annual Meeting (May 30 - June 3, 2014)
3. van der Velde G, Paulden M, Ieraci L, Wijeysundera H, Witteman W, **Krahn M**. Cost-effectiveness of Non-invasive Cardiac Imaging Technologies in Outpatients with Suspected Coronary Artery Disease. 33rd Annual Meeting of the Society of Medical Decision Making. *Medical Decision Making* 2012;32:E126-7.
4. van der Velde G, Paulden M, Ieraci L, Wijeysundera H, Witteman W, **Krahn M**. Cost-effectiveness of Non-invasive Cardiac Imaging Technologies in Outpatients with Suspected Coronary Artery Disease. 2012 CADTH (Canadian Agency for Drugs and Technologies in Health) Symposium 'Evidence Matters: Outcomes, Efficiency, Impact'. Conference Proceedings - Concurrent Oral Session B5 (Cardiovascular), page 39.
5. Chen W, Zagorski B, Krajden M, Heathcote J, **Krahn M**. Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. Canadian Journal of Gastroenterology 2009;23(Suppl A):6A
6. Naglie G, Borrie M, Black S, Beattie B, **Krahn M**, Irvine J, Hogan D, Bergman H, MacKnight C, Patterson C, Byszewski A, Freedman M, Streiner D, Ritvo P, Comrie J, Kowgier M, Tomlinson G. Predictors of quality of life in dementia caregivers. Journal of the American Geriatrics 2009; 57(S1):S107
7. John-Baptiste A, Tomlinson G, Hsu P, Krajden M, Heathcote J, Laporte A, Yoshida E, Anderson F, **Krahn M**. Quality of life following antiviral therapy for chronic hepatitis C virus infection. Canadian Journal of Gastroenterology. 2009;23(Suppl A):128A.
8. Johnson A, Levin L, **Krahn M**, Sikich N, Evans B, Pauldr O, Giacomin, Glendining, Evans G. Health Technology Assessment - A Comprehensive Framework for Evidence-Based Recommendations in Ontario. Int J Technology Assessment in Health Care 2009;25:3 .
9. Thein HH, Yi Q, Dore G, **Krahn M**. Natural history of hepatitis C in HIV-infected individuals and the impact of HIV in the era of HAART: a meta-analysis. Can J Gastroenterol 2008;22:(Suppl A), 75A.[Oral]
10. Chen W, Zagorski B, Krajden M, Heathcote EJ, **Krahn M**. Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. Hepatology 2008;47(4):120A
11. Chen W, Dinner K, Wong T, Heathcote J, **Krahn M**. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. Value of Health 2008;11(3):A92
12. John-Baptiste A, **Krahn M**, George Tomlinson. Natural History of Chronic HCV infection obtained through Injection Drug Use: A Bayesian Meta-Analysis. Value in Health. 2008;11(3):A92.
13. John-Baptiste A, Varenbut M, Lingley M, Nedd-Roderique T, Teplin D, Daiter J, **Krahn M**. Treatment of hepatitis C infection for current or former substance abusers in a community setting. Value in Health. 2008;11(3):A92.
14. John-Baptiste A, **Krahn M**, George Tomlinson. Natural History of Chronic HCV infection obtained through Injection Drug Use: A Bayesian Meta-Analysis. Canadian Journal of Gastroenterology. 2008;22(Suppl A):163A.
15. John-Baptiste A, Varenbut M, Lingley M, Nedd-Roderique T, Teplin D, Daiter J, **Krahn M**. Treatment of hepatitis C infection for current or former substance abusers in a community setting. Canadian Journal of Gastroenterology. 2008;22(Suppl A):164A.

16. John-Baptiste A, Grebely J, Genoway K, Gallagher L, Elliot D, **Krahn M**, Conway B. Quality of life and health values of injection drug users with chronic hepatitis C virus (HCV) infection. Canadian Journal of Gastroenterology. 2008;22(Suppl A):164A.
17. Toren P, Alibhai S, **Krahn M**, Kolnin R, Nesbitt M, Trachtenberg J, Matthew A. The effect of nerve-sparing surgery on patient-reported incontinence post-radical prostectomy. 63rd Annual Meeting of the Canadian Urological Association, Edmonton, Alberta June 23, 2008. To be published in Canadian Urological Association Journal (CUAJ).
18. Ku J, Alibhai S, **Krahn M**, Nesbitt M, Kolnin R, Fleshner N, Trachtenberg J. Changes in health related quality of life and health values over 12 months after radical prostatectomy. 63rd Annual Meeting of the Canadian Urological Association, Edmonton, Alberta June 23, 2008. To be published in Canadian Urological Association Journal (CUAJ).
19. Ku J, Trachtenberg J, **Krahn M**, Nesbitt M, Kolnin R, Fleshner N, Alibhai S. What is the rate of sexual recovery after radical prostatectomy? It depends on how one defines an erection. 63rd Annual Meeting of the Canadian Urological Association, Edmonton, Alberta June 23, 2008. To be published in Canadian Urological Association Journal (CUAJ).
20. Chen W, Wong T, Tomlinson G, **Krahn M**, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. Canadian J Gastroenterology. 2008;22(Suppl A):246A
21. Sander B, **Krahn M**. Influenza vaccine delivery programs: A systematic review. Poster presentation at the 2008 CADTH Symposium, Edmonton, Alberta, April 27-29, 2008.
22. Cantor SB, Volk RJ, , Cass AR, Gilani J, Weller SC, Spann SJ. Concordance of couples' prostate cancer screening recommendaions from a decision analysis. The patient 2008 Jan 1;1(1):11-19.
23. Naglie G, Comrie J, Beattie L, Bergman H, Black S, Borrie M, Byszewski A, Freedman M, Hogan D, Irvine J, **Krahn M**, MacKnight C, Patterson C, Ritvo P, Streiner D, Kowgier M, Tomlinson GF. Depressive symptoms and functional status predict quality of life in patients with Alzheimer's disease: Cross-sectional results from the Canadian Alzheimer's Disease Quality of Life (CADQOL) Study. Canadian Journal of Geriatrics 2008;11(1):38-39
24. Naglie G, Comrie J, Beattie L, Bergman H, Black S, Borrie M, Byszewski A, Freedman M, Hogan D, Irvine J, **Krahn M**, MacKnight C, Patterson C, Ritvo P, Streiner D, Kowgier M, Tomlinson GF. Depressive symptoms and functional status predict quality of life in patients with Alzheimer's disease: cross-sectional results from the Canadian Alzheimer's Disease Quality of Life (CADQOL) Study.CGS 2008 Meeting. Journal of the American Geriatrics Society 2008:56(S1):S2-S3.
25. Naglie G., Comrie J., Beattie L., Bergman H., Black S., Borrie M., Byszewski A., Freedman M., Hogan D., Irvine J., **Krahn M.**, MacKnight C., Patterson C., Ritvo P., Streiner D., Kowgier M. and Tomlinson G. Patient and Caregiver Quality of Life in Alzheimer's Disease in Relation to Dementia Severity. Journal of American Geriatrics Society. 2007;55(S1):S1-S2.
26. Chen W, Dinner K, Wong T, Heathcote J, **Krahn M**. A cost-effectivienss analysis of hepatitis C screening among immigrants in Canada. Canadian J Gastroenteroly. 2008;21(Suppl A):14A
27. Chen W, Dinner K, Wong T, Heathcote J, **Krahn M**. A cost-effectivienss analysis of hepatitis C screening among immigrants in Canada. Canadian Hepatology 2007;46(4):891A
28. John-Baptiste A, **Krahn M**, George Tomlinson. Natural History of Chronic HCV infection obtained through Injection Drug Use: A Bayesian Meta-Analysis. Canadian Journal of Gastroenterology. 2007;21(Suppl A):126A.
29. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JD, Côté P, **Krahn M**. Neck pain patients' evaluative scores for their current health state. 14th Annual Conference of the International Society for Quality of Life Research, October 10-13, 2007, Toronto, Canada. Quality of Life Research Supplement, A-111, Abstract #1800.
30. Anonychuk A, Gilca V, Pham B, Duval B, Bauch C, **Krahn M**. Burden and cost of hepatitis A infection in Canada. 7th Canadian Immunization Conference, Winnipeg Dec 3-6, 2006.
31. Tricco A, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, Anonychuk A, **Krahn M**, Moher D.

Published data underestimates the burden of hepatitis A intervention triggered by infected food handlers. 7th Canadian Immunization Conference, Winnipeg Dec 3-6, 2006

32. Sander B, Tomlinson G, **Krahn M**, The Cost-Utility Of Ontario's Universal Influenza Immunization Program, 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006.
33. Chen W, Wong T, Tomlinson G, **Krahn M**, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. Hepatology 2007;46(4):632A
34. Chen WD, Heathcote J, **Krahn M**. Primary prevention of esophageal variceal bleding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. Gastroenterology.2006;130(suppl 2)A811
35. Chen W, **Krahn M**. Review: Ribavirin is not better than placebo in chronic hepatitis C infection. ACP J Club 2006;145(2):47
36. Nelson E, Fraser G, Connors A, Barry M, **Krahn M**, Conaway M, Bashore R, Wolf A, Kilbridge K. Misunderstanding of Prostate Cancer (CaP) among African American (AA) Men of Lower Socioeconomic Status (Lo-SES), 2006 ASCO Annual Meeting, Atlanta, Georgia, June 2-6, 2006
37. Bauch C.T., Rao A, Pham B, **Krahn M**, Gilca V, Duval B, Chen M.H., Tricco A. Implications of universal hepatitis A vaccination in Canada: Predictions of a dynamic model. Ninth Annual Conference on Vaccine Research, National Foundation for Infectious Diseases; Baltimore May 8-10, 2006.
38. Chen WD, Heathcote J, **Krahn M**. Prevalence and predictors of high body mass index among native born and immigrant patients with chronic hepatitis C in Canada. Gastroenterology 2006;130(suppl 2):A780
39. Chen WD, Heathcote J, **Krahn M**. Primary prevention of esophageal variceal bleeding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. Can J Gastroenterol 2006;20(3):193
40. Menon D, **Krahn M**, Pham B. A tale of two university-based health technology assessment initiatives. CCOHTA Invitational Symposium, Ottawa 2006 (accepted).
41. Anonychuk A, Duval B, Bauch C, **Krahn M**, Pham B, Gilca V, Tricco A. Under-reporting of hepatits A case notification data in a low endemic country. Can J Gastroenterol 2006;20(3):193.
42. Anonychuk A, Duval B, Bauch C, **Krahn M**, Pham B, Gilca V, Tricco A. Methodological issues in cost effectiveness evaluation of hepatitis A vaccine: A systematic review. Can J Gastroenterol 2006;20(3):193.
43. Thein HH, Butler T, **Krahn M**, Rawlinson W, Levy M, Kaldor J, Dore G. The effect of hepatitis C virus infection on health-related quality of life in prisoners. Can J Gastroenterol 2006;20(3):211
44. Varenbut M, John-Baptiste J, Teplin D, Lingley M, Daiter J, **Krahn M**. Treatment of hepatitis C infection in patients on Methadone maintenance in a community setting. Can J Gastroenterol 2006;20(3): 212.
45. Bremner K, Bayoumi A, Sherman M, **Krahn M**. Management of solitary 1-2 cm liver nodules in patients with cirrhosis: a decision analysis. Can J Gastroenterol 2006;20(3):194.
46. **Krahn M**, Forde N, Mamdani M, Laporte A, Alibhai S, Bremner K, Tomlinson G, Naglie G. Design of longitudinal cost models for the prostate cancer policy model. Society for Medical Decision Making Annual Meeting, 2006;26(1):E31
47. Thein HH, Maruff P, **Krahn M**, Kaldor J, Koorey D, Brew B, Dore G. Cognitive and mood effects of antiviral therapy in HCV monoinfected and HIV/HCV coinfected individuals. Can J Gastroenterol 2006;20(3): 210.
48. Naglie G, Comrie J, Bacher Y, Beattie L, Bergman H, Black S, Borrie M, Byszewski A, Freedman M, Hogan D, Irvine J, **Krahn M**, MacKnight C, Patterson C, Ritvo P, Silberfeld M, Streiner D, Tomlinson G. Quality of life in Alzheimer's disease by severity level: Preliminary results from the Canadian Alzheimer's Disease Quality of Life (CADQOL) Study. The Canadian Journal of Geriatrics 2006;9:66.
49. Pham B, Tricco A, **Krahn M**. Markov Models for cost effectiveness analyses: A framework for assessing external consistency. SMDM Jan-Feb 2006:E7
50. Bauch C, Tricco A, Rao A, Gilca V, Duval B, Pham B, **Krahn M**. Evaluating periodicity of disease transmission prior to cost effectiveness evaluation of immunization programs. Medical Decision Making Jan-Feb 2006:E8
51. **Krahn M**, Forde N, Mamdani M, Laporte A, Alibhai S, Bremner K, Tomlinson G, Naglie G. Design of longitudinal cost models for the prostate cancer policy model. MDM Jan-Feb 2006:E31

52. Bremner K, Tomlinson G, Alibhai S, Laporte A, Naglie G, **Krahn M**. Effect of age on preferences for health outcomes in prostate cancer. MDM Jan-Feb 2006:E35
53. Sander B, John-Baptiste J, Maetzel A, **Krahn M**. Dynamic and cohort approaches to modeling influenza edidemics convergence or divergence? MDM Jan-Feb 2006:E39
54. Anonychuk A, Tricco A, Bauch C, Gilca V, Duval B, Pham B, **Krahn M**. Methodological issues in cost-effectiveness evaluation of hepatitis A vaccine: A systematic review. MDM Jan-Feb 2006:E69
55. Pham B, Bauch C, Chen M, Tricco A, Rao A, **Krahn M**. Use of catalytic modeling to estimate hepatitis A incidence in a low endemicity country: implications for modeling immunization policies. Pharmacoepidemiology and Drug Safety 2005:14:S138
56. Cohen JH, Faughnan ME, Letarte M, Vandezande K, Kennedy SJ, **Krahn M**. Cost comparison of genetic and clinical screening in families with hereditary hemorrhagic telangiectasis. Am J Med Genet A. 2005 Aug 30; 137(2):153-60.
57. **Krahn M**, Witkos M, Sanders G, Sugano D, Cantor S. What would make the society and the annual meeting better? A survey of the society for medical decision making membership. Medical Decision Making Jan-Feb 2005;25(1):E53.
58. Bremner K, Bayoumi A, Sherman M, **Krahn M**. Bipsy or resection for single small liver nodules in patitnes with compensated cirrhosis – A decision analysis. Medical Decision Making Jan-Feb 2005:25(1):E36.
59. Chen H, Bauch C, Foty R, Pham B, **Krahn M**. Use of catalytic modeling to estimate hepatitis A incidence in a low endemicity country: implications for modeling immunization policies. Medical Decision Making Jan-Feb 2005;25(1):E19.
60. Sander B, Naglie G, **Krahn M**, Maetzel A. Prevention or treatment of influenza in healthy adults – a cost-effective option for society? Medical Decision Making. July/August 2004;24(4):438.
61. Alibhai SMH, Leach M, Tomlinson G, **Krahn M**, Fleshner NE, Holowaty E, Naglie G. Complications after radical prostatectomy as a function of age, comorbidity and time. Journal of Urology 2004;171 (4 suppl.):216
62. Alibhai SMH, **Krahn M**, Cohen MM, Fleshner NE, Tomlinson G, Naglie G. What is the optimal comorbidity index for use in older people with cancer? Proc Int Soc Geriatr Oncol 2004; 5:119.
63. Leach M, Tomlinson G, Naglie G, **Krahn M**, Fleshner NE, Holowaty E, Alibhai SMH. Temporal trends in the treatment of prostate cancer in Ontario: 1990-1999. Geriatrics Today: J Can Geriatr Soc 2004; 7(3):109.
64. Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Black S, Freedman M, Silberfeld M, **Krahn M**. Validity of utility-based quality of life measures in Alzheimer's disease. The Gerontologist 2004;44(Special Issue 1):256.
65. Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Silberfeld M, **Krahn M**. Measuring quality of life and general health perceptions in Alzheimer's disease. The Gerontologist 2003;43(Special Issue 1):304
66. Bremner KE, Chong CAKY, Tomlinson G, **Krahn M**. A meta-analysisi fo utilities for prostate cancer. Medical Decision Making 2003;23(6):544.
67. Bremner KE, **Krahn M**. Do marker states improve the performance of direct utility measures? Medical Decision Making 2003;23(6):544.
68. John-Baptiste A, Cook T, Straus S, Naglie G, Tomlinson G, **Krahn M**. Economic and health consequences of a hyperbaric oxygen cchamber in the international space station. Medical Decision Making 2003;23(6):544.
69. Bremner KE, Tomlinson GA, Naglie G, Ritvo P, Irvine J, **Krahn M**. Prostate cancer patients' preferences for outcomes described by a multiattribute health state classification system for prostate cancer. Medical Decision Making. 22(6): 549, 2002 Nov/Dec
70. Chong CAKY, Naglie IG, **Krahn M**. Numer needed to mislead? NNT does not accurately predict health benefit or efficiency. . Medical Decision Making. 2002 Nov/Dec;22(6): 531
71. John-Baptiste A, Remis RS, Ritvo P, Doria AS, **Krahn M**. Estimating the potential cost-effectiveness of a preventive hepatitis C vaccine. . Medical Decision Making. 2002 Nov/Dec 22(6):534
72. Bremner KE, Tomlinson GA, Naglie G, Ritvo P, Irvine J, **Krahn M**. Predictors of prostate cancer patients' utilities for outcomes described by a multiattribute health state classification system for prostate cancer. Medical Decision Making. 22(6): 559, 2002 Nov/Dec.
73. Tomlinson GA, Bremner KE, Naglie G, Ritvo P, Irvine J, **Krahn M**. Development and validation of a

multi-attribute utility function for a multiattribute health state classifcation system for prostate cancer. Medical Decision Making. 22(6): 560, 2002 Nov/Dec

74. Bremner KE, Naglie G, Tomlinson G, Ritvo P, Irvine J, **Krahn M**. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. Medical Decision Making 2001; 21: 525.
75. Tzanetos K, Cavalcanti R, **Krahn M**. Optimal lengthe of anticoagulation after a first episode of idiopathic venous thromboembolism. Medical Decision Making 2001; 21: 517.
76. Alibhai SMH, **Krahn M**, Gohen MM, Fleshner NE, Naglie G. Does patient age influence prostate cancer tumour severity at diagnosis? Gerontology 2001;47(Suppl 1):476-477.
77. **Krahn M**, Wong J, Heathcote J, Scully L, Seeff L. Allocating funds from a national compensation agreement using Markov modeling: the cae of the 1986-90 post-transfusion hepatitis C victims. Medical Decision Making 2001; 21: 527.
78. Jong P, Lee D, Liu PP, **Krahn M**. Cost-effectiveness of carvedilol versus standard care in the treatment of mild to moderate heart failure. Medical Decision Making 2001; 21: 538.
79. Maetzel A, **Krahn M**, Naglie G. Short-term pain for long-term gain: alternate approaches to incorporation of short-term utilities into cost-utility analyses. Medical Decision Making 2001; 21: 541.
80. **Krahn M**, Sherman M, Hogg R, Remis R, Zhou S, Wu J. Universal hepatitis A vaccination for adolescents and children in Canada: a cost-effectiveness and cost-utility analysis. Medical Decision Making 2001; 21: 542.
81. Chong C, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, **Krahn M**. Health-state utilites and quality of life in hepatitis C patients. Medical Decision Making 2001; 21: 525.
82. **Krahn M**, Wong J, Heathcote J, Scully L, Seeff L. Allocating funds from a national compensation agreement using Markov modeling: the cae of the 1986-90 post-transfusion hepatitis C victims. Medical Decision Making 2001; 21: 527.
83. Jong P, Lee D, Liu PP, **Krahn M**. Cost-effectiveness of carvedilol versus standard care in the treatment of mild to moderate heart failure. Medical Decision Making 2001; 21: 538.
84. Maetzel A, **Krahn M**, Naglie G. Short-term pain for long-term gain: alternate approaches to incorporation of short-term utilities into cost-utility analyses. Medical Decision Making 2001; 21: 541.
85. **Krahn M**, Sherman M, Hogg R, Remis R, Zhou S, Wu J. Universal hepatitis A vaccination for adolescents and children in Canada: a cost-effectiveness and cost-utility analysis. Medical Decision Making 2001; 21: 542.
86. Naglie G, Tansey C, **Krahn M**, Irvine J, Ritvo P, Tomlinson G, Silberfeld M. Evaluation of three generic utility-based quality of life measures in Alzheimer's disease. Gerontology 2001;47(Suppl 1):526.
87. Alibhai S, **Krahn M**, Gohen M, Fleshner N, Naglie G. Does patient age influence prostate cancer tumour severity at diagnosis? Gerontology 2001;47(Suppl 1):476-477.
88. Maetzel A, **Krahn M**, Naglie G. The cost-effectiveness of celecoxib and rofecoxib in patients with osteoarthritis or rheumatoid arthritis. Arthritis & Rheumatism 2001;44(Suppl. 9):
89. Alibhai SMH, **Krahn M**, Cohen MM, Fleshner NE, Naglie G. Older patients receive less aggressive treatment for clinically localized prostate cancer. Clinical and Investigative Medicine 2000; 23(5):332.
90. Alibhai S, Nam R, Naglie G, Trachtenberg J, **Krahn M**. Influence of age, comorbidity, and source of efficacy data on optimal treatment choice for localized prostate cancer: a decision analytic view. Clinical and Investigative Medicine 2000; 23(5):331-332.
91. **Krahn M**, Ritvo P, Naglie IG, Irvine J, Trachtenberg J. Utilities in prostate cancer: implications for clinical and health policy. Clinical and Investigative Medicine 1999.
92. **Krahn M**, Wong J, Heathcote EJ, Scully L, Seeff L. Prognosis of post transfusion hepatitis C virus infection. Clinical and Investigative Medicine 1999.
93. **Krahn M**, Ritvo P, Naglie I, Irvine J, Trachtenberg J. Patient and population preferences for outcomes in prostate cancer. Medical Decision Making. 1998;18:472.

94. **Krahn M**, Guasparini R, Sherman M, Detsky AS. Costs and cost effectiveness of a universal adolescent hepatitis B vaccination program in British Columbia. Podium presentation, Royal Collegé of Physicians and Surgeons annual meeting. Clinical and Investigative Medicine 1997).
95. **Krahn M**, Ritvo P, Naglie IG, Irvine J, Trachtenberg J. Construction of a multiattribute utility instrument for prostate cancer. Medical Decision Making. 1997;17:528.
96. Naglie G, **Krahn M**, Tansey C, Bolley H, Detsky A. Cost utility analysis of coronary bypass surgery versus medical therapy in the elderly. Medical Decision Making. 1997;16:442.
97. Naglie G, Tansey C, **Krahn M**. Seniors' preferences for chronic health states: utility assessments of heart disease, stroke, and dementia. Medical Decision Making. 1997;17:521.
98. Naglie G, **Krahn M**, Tansey C, Bolley H, Detsky A. Cost-Utility Analysis of Coronary Artery Bypass Surgery Versus Medical Therapy in the Elderly. Medical Decision Making 1997;16:442.
99. Bloomfield DJ, Tannock IF, **Krahn M**. Should Luteinizing Hormone Releasing Hormone (LHRH) Agonists be Continued in the Presence of Hormone Refractory Metastatic Prostate Cancer? A Decision Analysis. Medical Decision Making 1996;16:470.
100. **Krahn M**, Naglie IG, Irvine J, Ritvo P, Trachtenberg J. Patient and expert quality of life ratings in the construction of an empirically devised domain linked utility instrument for prostate cancer. Medical Decision Making 1996;16:470.
101. Naglie G, Tansey C, Bolley H, **Krahn M**, Detsky A. Coronary Bypass Surgery in the Elderly: How Much Does It Cost? Journal of the American Geriatric Society 1995; 43: SA53.
102. Naglie G, Tansey C, Bolley H, **Krahn M**, Detsky A. An Itemized Costing of Coronary Artery Bypass Surgery in the Elderly. The Toronto Hospital and The University of Toronto. Clinical and Investigative Medicine 1995 (Suppl);18:B61.
103. **Krahn M**, Detsky AS. Costs and cost effectiveness of British Columbia's grade six hepatitis B vaccination program. Medical Decision Making 1995;15:433
104. Taylor MC, **Krahn M**, Langer B, Taylor B. The management of liver metastases from colorectal cancer-a decision analysis. Medical Decision Making 1995;15:433.
105. **Krahn M**, Mahoney J, Eckman M, Detsky AS. PSA Screening for prostate cancer: a decision analytic perspective Journal of Urol 1993; 148:299A.
106. **Krahn M**, Detsky AS. Universal Vaccination for Hepatitis B in North America. Clinical Research; 39:379A, 1991.
107. **Krahn M**, Naylor CD, Basinski AS, Detsky AS. Quality of Life and Cholesterol Policy. Clinical Research; 38: 282A, 1990.

Guidelines

1. Mittmann N, Evans W.K., Rocchi A, Longo C.J., Au H.J., Husereau D., Leighl N., Isogai P., **Krahn M**, Peacock S, marshall D, Coyle D, Malfair Taylor S.C., Jacobs P, Oh P.I. Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009

Letter (Correspondence)

1. Alibhai S, Leach M, Tomlinson G, **Krahn M**, Fleshner N, Holowaty E, Naglie G. 30 day mortality and major complications after radical prostatectomy: Influence of age and comorbidity. *J Natl Cancer Inst*. 2006 Mar 15;98(6):421-2.

Invited Lectures

A. National / International:

1. Introduction to Health Technology Assessment. SMDM Asia Pacific, Singapore, January 6, 2014
2. Plenary Speaker, Applied Research Conference in Cancer Control (ARCC) 2013, Vancouver, May 27, 2013
3. Panel Discussion, CADTH 2013, St. Johns, NL, May 5, 2013, won for "Best Idea"
4. Keynote speaker, Canadian Symposium on Hepatitis C Virus. Victoria, BC. March 4, 2013
5. HTA Institute: Health Technology Assessment for Decision Maker. Beijing University, Sept 12 -14, 2012, Beijing, China.
6. Health Technology Assessment in Ontario. European SMDM, Oslo Norway, June 12, 2012
7. 2011 CISNET Annual Meeting, Natcher Conference Center in Bethesda, MD
8. 2010 Annual Meeting of the Canadian Agency for Drugs and Technologies in Health (CADTH), Halifax
9. End of life care for elderly patients with advanced lung cancer in Ontario and the Uniited States. 2010 Annual Canadian Association for Health Services and Policy Research (CAHSPR) Conference. Toronto, ON May 10-13, 2010
10. Keynote address - 2010 Annual Meeting of the Canadian Association for Population Therapeutics (CAPT), Toronto, March 28-30.
11. Relative influence of treatment and prevention strategies on mortality: The Ontario experience. Canadian Cardiovacular Society, Edmonton, AB, Oct 24-28, 2009.
12. Modeling best practice to treat small HCC. 60th Annual Meeting AASLD Symposium, Boston MA, USA, Oct 30-Nov 3, 2009.
13. Collaboration between HTA agency and health authority: Ontario Canada. 6th Annual meeting HTAi Globalisation and Health Technology Assessment. Singapore June 21-24, 2009.
14. Effect of age on preferences for health outcomes in prostate cancer. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007.
15. The patient-oriented prostate utility scale (PORPUS-U_i) – a prostate cancer-specific utility instrument. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007.
16. Predictors of life-time and stage-specific costs of prostate cancer. ASCO The Prostate Cancer Symposium, Orlando, Florida, February 22-24, 2007
17. Decision analysis in prostate cancer outcomes assessment. ASTRO Health Services Research Meeting, October 2006, San Diego.
18. Economic evaluation in the assessment of new vaccines. Journees Annuelles de Sante Publique. October 2006, Montreal.
19. Health technology assessment in Canada: problems and opportunities. Canadian Association for Population Therapeutics 2006, Toronto
20. Age-thresholds for prostate cancer screening. Iowa Department of Public Health Consensus guidelines meeting, April 2005
21. Burden of illness in HCV infection. National planning meeting for HCV-related behavioural research. February 2003, Toronto
22. Screening for hepatocellular carcinoma. AASLD Screening Workshop, Atlanta, February 2003
23. Economic evaluation of cancer screening programs. Cape Breton Regional Cancer Symposium. Cape Breton, NS, October 2001
24. Quality of life and economic outcomes in localized prostate cancer. ASTRO Consensus Development Meeting, San Francisco, October 2001.
25. Prostate cancer; is there value in treatment. Prostate Cancer Symposium, Whistler, BC, March 2000.
26. Uncertainty in prostate cancer. Prostate Cancer Symposium Whistler, BC.
27. WHO task force on neck pain scientific meeting: Decision analysis, an introduction. Toronto, September 1999.
28. "Principles of decision analysis." American Academy of Orthopedic Surgeons short course on Outcomes, Measurement, and Effectiveness, Chicago, July 1998.

29. "Utility Aspects of Quality of Life Measurement in Prostate Cancer." Prostate, Lung, Colorectal, and Ovarian (PLCO) Trial Investigators' Quality of Life Meeting. National Institutes of Health, Bethesda, Maryland, April 1995.
30. "Screening for Prostate Cancer: A Decision Analytic View." Medical Grand Rounds Englewood Hospital and Medical Center, Englewood, New Jersey, USA. May, 1995.
31. "Conservative Treatment of Localized Prostate Cancer." Medical Advisory Council on Urology Annual Meeting. Carmel CA, April 1994.
32. "Issues in COPD Screening: A Decision Analytic View." COPD 1992: Second
33. "A Clinician's Guide to Cost Effectiveness" Group Health Association of America Annual Meeting, February 1991.
34. "Quality of Life Issues in Cholesterol Lowering," National Heart, Blood, and Lung Institute Conference on Cholesterol Lowering in Adults, Sept. 1990.

B. Provincial:

1. Developing a Values Based Framework for Decision Making in Technology Assessment (and Health). CADTH Lecture Series. March 12, 2015, Ottawa, ON.
2. HTA Institute: Health Technology Assessment for Decision Maker. Dalhousie University. July 14 - 16, 2014.
3. Panel Discussion: HTA Guidance: Key factors that lead to favorable assessments. 3rd Annual Medical Device Innovation & Market Access Strategies in Canada. May 1-2, 2014, Ottawa.
4. Economic Model. CADTH HepC Workshop April 25, 2014, Ottawa, ON
5. HTA Institute: Health Technology Assessment for Decision Maker. University College July 26-28, 2013, Toronto, Ontario
6. Symposium on early HTA, CADTH May 5- 7, 2013, St. John's, Newfoundland.
7. Opportunities for Collaboration over the Lifecycle of Health Technologies. CADTH Board of Directors Retreat, September 26, 2012
8. HTA Institute: Health Technology Assessment for Decision Maker. Medical Science Building, University of Toronto, July 25 - 27, 2012, Toronto, Ontario
9. "Costs for End-of-Life Care for Elderly Patients with Advanced Lung Cancer in Ontario" Canadian Cancer Research Conference November 2011
10. HTA Institute: Health Technology Assessment for Decision Maker. University of Toronto, July 20- 22, 2011, Toronto, Ontario
11. "Paradigms in Health Technology Assessment" BCCDC April 3, 2009
12. "Conditionally funded field evaluations in Ontario" 2009 CADTH Invitational Symposium, March 17, 2009
13. "Three scientific paradigms in health technology assessment: Experiences of the committee to evaluate drugs in Ontario." 2007 CADTH Invitational Symposium, April 2007
14. "The concept of cost-efficiency in immunization programs." 10th JASP Symposium, Monteal, October 2006
15. "Modeling outcomes in prostate cancer". Issues and Controversies in Prostate Cancer Care. Whistler, BC., March 1999.
16. "Risk, uncertainty, and decision-making in prostate cancer". Issues and Controversies in Prostate Cancer Care. Whistler, B.C., March 1999
17. "Introduction to decision analysis." Institute of Pharmacoeconomics short course, Calgary, Alta, January 1998.

18. "Screening for Prostate Cancer," Grand Rounds, St. Paul's Hospital, Vancouver, November 1994.
19. PSA Screening for Prostate Cancer." Canadian Urological Association annual meeting, Quebec City, March 1993
20. "The Cost of Asthma in Canada." Atlantic Respirology Conference, Halifax, November 1993.
21. "Cost Effectiveness of Universal Hepatitis B Vaccination." Society of Community Medicine and Public Health of Quebec, November 1991.
22. "Cost Effectiveness of Universal Hepatitis B Vaccination of Neonates," National Advisory Committee on Immunization, Ottawa, April 1990.

C. Local:

1. Health Technology Assessment in Ontario. Clnical Epidemiology Synthesis Sessions, March 23, 2015 or April 20, 2015, Toronto, Ontario
2. Health Technology Assessment in Ontario (and UHN). General Internal Medicine/Geriatrics Division Grand Rounds. February 19, 2015, Toronto, ON
3. Research Development Advisory Committee. Emerging health services research at UHN. Collaborative Academic Practice (CAP). UHN Research, February 18, 2015, Toronto, ON
4. Health Technology Assessment: Evidence, cost-effectiveness and social value. Cancer Care Ontario Prevention Intervention Workshop, January 28, 2015, Toronto, Ontario
5. Evaluation of complex health interventions. Baycrest Geriatric Medicine Rounds. December 4, 2014, Toronto, Ontario.
6. Sleep Apnea screening and smoking cessation. Yogendran memorial lecture grand round. October 3, 2014, Toronto Western Hospital, Toronto, Ontario
7. Systematic review on treatment decision-making for older adults with Cancer. February 10, 2014 Hart House, Toronto, ON
8. End-of-life Care, 6th Annual THETA Symposium, May 30, 2013, Toronto Ontario
9. Vaccine Pharmacoeconomics Workshop, November 25, 2013. Toronto.
10. Living with Myeloproliferative Neoplasms: Quality of Life Indicators and Survey. Canadian MPN Network Patient & Family Support Day, November 10, 2013. Toronto
11. Health Techology Assessment in Ontario. TGRI Research Day. Toronto, October 8, 2013.
12. Sunnybrook Health Sciences GIM Noon Rounds, Toronto, February 25, 2013
13. HTA Aspects of Evaluation of Robotic Surgery. Robotic Surgery Retreat. Toronto, February 1, 2013.
14. Health Technology Assessment in Ontario, SMH clinical and Population Research Rounds. Toronto, January 17, 2013.
15. Health Technology Assessment in Ontario. UTM Guest Lecture, September 25, 2012. Toronto
16. Knowlege Translation to Policy: Chronic Wound Prevention & Wound Care Delivery. THETA 3rd Annual KT Symposium, May 10, 2012, Toronto, ON
17. Challenges of Quality, Evidence and Patient-Centered Care. IHPME Research Day, May 2, 2012, Toronto
18. Knowlege Translation to Policy: Cardiovascilar Research & Personalized Medicine. THETA 2nd Annual KT Symposium, May 13, 2011, Toronto, ON
19. Knowlege Translation to Policy: Wound Care and Cardiovascular Research. THETA 1st Annual KT Symposium, May 27, 2010, Toronto, ON
20. Three scientific paradigms in health technology assessment. Sigma Xi Distinguished Lecture Series, University of Toronto. November 26, 2009, Toronto, ON.
21. Three paradigms in Health Technology Assessment: How decisions are made about funding new drugs and

other technologies. East End Community Health Centre Annual General Meeting, June 17, 2009, Toronto, ON.

22. Field Evaluations in HTA, Second Annual THETA Symposium, May 22 - 24, 2009, Niagara-on-the-Lake, Ontario
23. Paradigms in Health Technology Assessment. HCTP Annual Interdisciplinary Workshop
24. March 26-27, 2009 St. Andrew's Club & Conference, Toronto, ON
25. "Conditionally funded field evaluations in Ontario." HPME city-wide clinical epidemiology rounds March 25, 2009.
26. "Pharmacists and Pharmacoeconomics." Leslie Dan Faculty of Pharmacy, University of Toronto, March 2006
27. Are "cost effectiveness" analyses of value in determining cancer drug funding. Cancer systemic therapy search conference, McLean House, The estates of Sunnybrook, September 2005
28. "Prevalence and predictors of high body mass index among native born and immigrant patients with chronic hepatitis C." Research Day, Toronto 2005
29. "The cost-utility of Ontario's universal influenza immunization program (UIIP)." Research Day, Toronto 2005.
30. Health economics, outcomes research, and health services research in prostate cancer. Bierstock lecture. Toronto, September 2001.
31. "Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada between 1986 and 1990", Grand Rounds, the Toronto General Hospital, May 2000.
32. "Decision sciences and economic evaluation." Cardiology trainees, The Toronto Hospital, February 1999.
33. "The Value of Treatment in Prostate Cancer: The Role of Decision Models in Clinical Policy and Patient/Physician Decision Support." Opening of the Prostate Centre, University Health Network, Toronto, September 1999.
34. Modeling hepatitis C outcomes." Canadian Association for the Study of the Liver Conference on hepatitis C prognosis, Toronto, September 1998.
35. "PSA Screening for Prostate Cancer." 1st Annual Retreat, Department of Preventive Oncology, University of Toronto, Toronto, May 1997.
36. "Principles of Economic Evaluation in Screening Programs," invited seminar, annual meeting of the Canadian Society for Epidemiology and Biostatistics, London, Ontario, May 1997.
37. "Cost Effectiveness of Spirometric Screening for COPD," COPD Round Table, Toronto, Ontario, May 1996.
38. "Principles of Health Economics," Palliative Care Rounds, the Toronto Hospital, February 1996
39. "Uncertainty," Grand Rounds, The Toronto Hospital, Western Division, March 1996
40. "Cost Effectiveness of Hepatitis B Vaccination," Grand Rounds, The Toronto Hospital, April 1996.
41. "PSA Screening for Prostate Cancer," Grand Rounds, The Toronto Hospital, Western Division, Toronto, February 1995.
42. "PSA Screening for Prostate Cancer: A Decision Analytic View." Rounds at the National Cancer Institute, Bethesda, Maryland, April 1995.
43. "Biochemical Screening for Prostate Cancer." Ontario Medical Association Annual Meeting , Section on Laboratory Medicine and Hematology /Medical Oncology. Toronto, May 1995.
44. "PSA Screening for Prostate Cancer," Grand Rounds, The Toronto Hospital, General Division, Toronto, May 1995.
45. "Screening for Prostate Cancer: A Decision Analytic View." Laboratory Medicine Series. Telemedicine Canada, Toronto, June 1995.

46. "Cost Effectiveness of BC's Grade Six HBV Vaccination Program." Telemedicine Canada. Toronto, October 1995.
47. "A Decision Analytic View of PSA Screening for Prostate Cancer." Mount Sinai Hospital, Grand Rounds. Toronto, November 1995.
48. "Principles of Economic Evaluation in Cancer Screening." Citywide Clinical Biochemistry Rounds, Mount Sinai Hospital, Toronto, November 1995.
49. "New Research Findings in Screening and Treatment for Prostate Cancer." Minisymposium: Advances in PSA. Division of Clinical Biochemistry, University of Toronto. November, 1995.
50. "Screening for Prostate Cancer." Ontario Cancer Treatment and Research Foundation Annual Research Symposium. Toronto, April 1994.
51. "Guidelines for Hepatitis B Vaccination in Childhood." Canadian Task Force on the Periodic Health Examination. Toronto, April 1994.
52. "Dying with or Dying from Prostate Cancer: A Decision-Analytic View of the Screening Question." Proceedings of the OCTRF Cancer Epidemiology Seminar. Toronto, April, 1994.
53. "Screening for Prostate Cancer," Grand Rounds, Wellesley Hospital, Toronto. October 1994.
54. "The Debate on Prostate Cancer Screening," presentation to Friends of the University of Toronto, Gluskin, Scheff and Associates, Toronto. November 1994.
55. "Quality of Life, Patient Empowerment, and Decision Support in Prostate Cancer," NCIC Forum, Toronto, February 1994.
56. "PSA Screening for Prostate Cancer." American Academy of Insurance Medicine Annual Meeting, Toronto, September 1993.
57. "PSA Screening for Prostate Cancer," OMA Section on Family Practice meeting, Toronto, May 1993
58. "Screening for Prostate Cancer: A Decision Analytic View." Ontario Society of Clinical Biochemists Annual Meeting, North York, Ontario. October 1993.
59. "The Cost Effectiveness of Asthma Education." First Annual Conference on Asthma and Education. Toronto, November 1993.
60. "Decision Support for Localized Cancer Treatment Decisions." Prostate Centre anniversary, Toronto, March 1993.
61. Annual Conference on COPD in Canada. Toronto, June 1992.
62. "PSA Screening for Prostate Cancer." University of Toronto CME Prostate Cancer Symposium, Toronto, September 1992

Presentation and Special Lectures

1. Seattle Panel Meeting. Seattle, WA February 11- 13th, 2015
2. **Krahn M**, Miller F, Bayoumi A, Giacomini M, Goeree R, Wagner F, Winsor S, Schunemann H, van de Velde G, Pham B, Petersen S, Brooker AS, Rac V. Improving the appraisal of non-drug technologies: Revising the Ontario Decision Framework. 2015 CADTH Symposium Apr 12 -14, TCU Place in Saskatoon, SK. [accepted for panel session]
3. Rac V, Abrahamyan L, **Krahn M**. Complex interventions for comparative effectiveness and health technology assessment. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for 1/2 day workshop)
4. **Krahn M**, Wong W. Public policy in the post-interferon era: Can we afford to cure Hepatitis C? 2015 CADTH Syposium April 12 - 14, TCU Place in Saskatoon, SK [accepted for panel sessions].
5. Wong W, Feld J, **Krahn M**. Cost-effectiveness of a one-time national hepatitis C screening program: impact of a selective drug reimbursement policy. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted oral presentation)
6. Miller F, Barg C, **Krahn M**, Lehoux P, Peacock S, Rac V. Two solitudes: HTA and procurement as

pathways to the adoption of health technologies. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for oral presentation)

7. Rac V, Wong J, Mitsakakis N, Haratsidis E, **Krahn M**. Implementation challenges of a community-based pragmatic randomized controlled trial in wound care. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
8. Mitsakakis N, Bremner K, **Krahn M**. Benefits of transformations in mapping health utilities. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
9. Pechlivanoglou P, Abrahamyan L, Pham B, Hsu S, Paulden M, **Krahn M**. Projecting mortality rates in economic evaluation: A simulation study. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
10. Pham B, Fowler R, Tanuseputro P, Manuel D, Sikich N, Baidoobonso S, Pechlivanoglou P, Levin L, Guerriere D, Coyte P, **Krahn M**. Including the patient's family in cost-effectiveness analysis of end-of-life interventions. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
11. Xie X, Wang M, Schaink A, **Krahn M**. Pulmonary rehabilitation for post-acute exacerbations of chronic obstructive pulmonary disease: A cost-effectiveness and budget impact analysis. 2015 CADTH Symposium April 12-14, TCU Place in Saskatoon, SK [accepted for poster presentation)
12. Tadrous M, mamdani MM, Juurlink DN, **Krahn M**, Levesque LE, Cadarette SM. Looking both ways before using the Disease Risk Score (DRS): Performance of the DRS in a cohort with known selection bias. International Conference in Pharmacoepidemiology and Therapeutic Risk Management Annual Meeting. October 2014, Taipei, Taiwan [poster presentation]
13. Rac V, Abrahamyan L, **Krahn M**. Complex interventions for comparative effectiveness and health technology assessment. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. (1/2 day short course teaching)
14. Pechlivanoglou P, Abrahamyan L, Pham B, Paulden M, **Krahn M**. The impact of estimating mortality rates in cost-effectiveness analysis: A simulation study. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [oral presentation]
15. Pham B, Fowler R, Tanuseputro P, Manuel D, Sikich N, Baidoobonso S, Pechlivanoglou P, Levin L, **Krahn M**. Cost-effectiveness analysis of palliative team care for patients nearing end-of-life. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [oral presentation]
16. Muhlberger N, Heijnsdijk E, Kurzthaler C, **Krahn M**, Oberaigner W, Klocker H, Conrads-Frank A, Sroczynski G, Siebert U. The oncotyrol prostate cancer outcome and policy model-lessons learned from natural history calibration. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[oral presentation]
17. Wong W, Feld J, Wong T, **Krahn M**. Cost-effectiveness of screening hepatitis C in Canada. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
18. Wong W, Hicks L, Tu HA, **Krahn M**, Pritchard K, Feld J, Chan K. Cost-effectiveness of hepatitis B virus screening before adjuvant chemotherapy in patients with early stage breast cancer. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
19. Nanwa N, Kendzerska T, **Krahn M**,. Kwong J, Daneman N, Witmann W, Mittmann N, Cadarett S, Rosella L, Sander B. The economic impact of clostridium difficile: A systematic review. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
20. Rac V, Wong J, Mitsakakis N, Pechlivanoglou P, Carcone S, **Krahn M**. Wound Interdisciplinary Teams (WIT): A community-based pragmatic randomized controlled trial. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
21. Wong J, Rac V, Mitsakakis N, Haratsidis E, **Krahn M**. Implementation challenges of a community-based pragmatic randomized controlled trial in wound care. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. (poster presentation)
22. Nanwa N, Kwong J, **Krahn M**, Daneman N, Lu H, Govindarajan A, Rosella L, Cadarette S, Sander B. Adopting the phase-of-care approach to estimate costs of a secondary diagnosis of clostridium difficile.

The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]

23. Jiang M, Pechlivanoglou P, Wong J, Mitsakakis N, Carcone S, Pham B, Rac V, **Krahn M**. Cost-effectiveness analysis of systmatic referral to multidisciplinary wound care teams in Ontario. Evidence from teh wound interdisciplinary teams (WIT) trial. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL.[poster presentation]
24. Tawfik A, Wodchis W, Hoch J, **Krahn M**. Estimating healthcare costs for decision-analytic models in atrial fibrillation using administrative data. The 36th Annual Meeeting of the Society for Medical Decision Making October 18-22, 2014. Miami, FL. [poster presentation]
25. Tadrous M, Mamdani MM, Juurlink DN, **Krahn M**, Levesque LE, Cadarette SM. Looking both ways before using the Disease Risk Score (DRS): Performance of the DRS in a cohort with known selection bias. Canadian Association of population Therapeutics Annual Conference. November 2014, Toronto ON, Canada [poster presentation]
26. Tu HA, Deeks S, Morris S, Strifler L, Crowcroft N, Jamieson F, Kwong J, Coyte P, **Krahn M**, Sander B. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for poster presentation).
27. Boehme K, Perlis N, Finelli A, Alibhai S, Kulkarni G, **Krahn M**, Bremner K. Developing the Bladder Utility Symptom Scale (BUSS): A multiattribute health state classification system for bladder cancer. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for poster presentation).
28. Wijeysundera H, Wang X, Bennell M, Ko D, Abrahamyan L, Tu J, Austin P, **Krahn M**. Characteristics of multi-disciplinary heart failure clinics that predict 1-year cumulative health care costs; a population-based study. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for oral presentation).
29. Wong W, Tu HA, Chen W, Feld J, Chelak K, Lee K, **Krahn M**. The hepatitis C drug pipeline: collaboration between academic and HTA agency partners to develop an early economc model. The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore MD. October 19-23, 2013 (accepted for oral presentation).
30. Bermingham S, Chandra K, Masucci L, Ieraci L, Chan B, Goeree R, **Krahn M** Seven months to complete seventy cost-effectiveness analyses! How to achieve the impossible using administrative data. HTAi. June 2013. Seoul [poster presentation]
31. Miller F, **Krahn M**, Levin L, Pham B, and Rac VE. Early Health Technology Assessment and Sustained Innovation. Panel Discussion. CADTH Meeting. St. John, New Foundland, May 2013
32. L Abrahamyan, Wijeysundera HC, **Krahn M**, Rac VE. Exploring Gender Bias in Heart Failure Patients Treated in Specialized Multi-Disciplinary Ambulatory Clinics of Ontario. CIHR YI Forum, Toronto, Canada. May 27-29, 2013 (poster presentation)
33. Mitsakakis N., Bremner K., and **Krahn M**. Methodological challenges in mapping a disease specific psychometric instrument to a disease specific utility instrument, Oral Presentation. 41st Annual Meeting of the Statistical Society of Canada, Edmonton, May 26-29, 2013
34. Mitsakakis N., Bremner K., and **Krahn M**. Methodological challenges in mapping a disease specific psychometric instrument to a disease specific utility instrument [poster]. ISPOR 2013, New Orleans. May 20th 2013
35. Miller F, **Krahn M**, Levin L, Pham B, and Rac VE. Early Health Technology Assessment and Sustained Innovation. Panel Discussion. CADTH Meeting. St. John, Newfoundland, May 2013.
36. **Krahn M.** Lessons learned from a cross-validaton between a discrete-event simulation model and a Markov Model for personalized breast cancer treatment. ISPOR 15th Annual European Congress November 3-7, 2012, Berlin, Germany.
37. Sander B, Ormanidhi O, Paszat L, Atkin K, Murphy J, **Krahn M**, Deeks S. The cost-effectiveness of integrated cervical cancer prevention strategies in the Ontario setting - can we do better? The 34th annual meeting of the Society for Medical Decision Making, Phoenix AZ. October 17 - 20, 2012 (Oral presentation).
38. Bremner K, **Krahn M**, Yabroff R, Hoch J, Barbera L, Liu N, Barrett M, Warren J. Opportunities and challenges in using administrative data for cross-country comparisons of health care costs. The 34th annual

meeting of the Society for Medical Decision Making, Phoenix AZ. October 17 - 20, 2012 (Poster presentation)

39. Tawfik A, Wodchis W, Hoch J, **Krahn M**. Cost-effectiveness of stroke prevention therapies in atrial fibrillation patients: A new generation of drugs. The 34th annual meeting of the Society for Medical Decision Making, Phoenix AZ. October 17 - 20, 2012 (Poster presentation)
40. **Krahn M.** Economic evaluation of mono and sequential hormone therapies for ER+ women with early breast cancer in Canada. ISPOR 15th Annual European Congress November 3-7, 2012, Berlin, Germany.
41. Bremner KE, **Krahn M**, Yabroff KR, Hoch J, Barbera L, Liu L, Barrett MJ, Warren JL. Opportunities and challenges in using administrative data for cross-country comparisons of health care costs. 34th Annual Meeting of the Society for Medical Decision Making, October 17-20, 2012 in Phoenix, Arizona, USA
42. **Krahn M**, Bremner KE, Luo J, Alibhai S. Using Administrative Databases to Estimate Health Care Costs from Adverse Drug Effect: The Case of Prostate Cancer. Biennial Society for Medical Decision Making European Meeting. June 10 - 12, 2012. Institute of Health Management and Health Economics, University of Oslo, Oslo, Norway
43. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M**. Evaluation of Trends in the Cost of Initial Cancer Treatment in Ontario. Canadian Association of Health Services and Policy Research, Montreal Quebec. May 29-31,2012
44. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M**. First-year Costs of Cancer Care in Ontario. Canadian Centre for Applied Research in Cancer Control Conference, May 28, 2012. Montreal Quebec
45. Paulden M, Franek J, Pham B, **Krahn M.** Gene expression profiling for guiding adjuvant chemotherapy decisions in women with early breast cancer. HOPE Research Centre, Sunnybrook Research Institute, Toronto, Ontario, Canada, 24 May 2012.
46. de Oliveira C, Bremner K, Gunraj N, Chan K, **Krahn M.** Using Administrative Health Care Data to Inform Cancer Care Research and Policy: Estimating the Economic Burden of Disease. Ontario Institute for Cancer Research/Cancer Care Ontario 4th Annual Meeting, May 17, 2012. Toronto.
47. **Krahn M**, Bremner KE, Luo J, Alibhai S. Using Ontario Administrative Data to Estimate Health Care Costs of Drug Adverse Effects: The Case of Prostate Cancer. Fourth Annual Meeting of the Ontario Institute for Cancer Research/ Cancer Care Ontario Health Services Research Program. May 17, 2012
48. van der Velde G, Paulden M, Ieraci L, Wijeysundera H, Witteman W, **Krahn M.** Cost-effectiveness of Non-invasive Cardiac Imaging Technologies in Outpatients with Suspected Coronary Artery Disease. 2012 Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium, April 15 – 17, 2012, Ottawa, Canada [Concurrent Oral Session B5 (Cardiovascular) – April 16, 2012].
49. Schieir O, Hincapie CA, Cote P, Hogg-Johnson S, Paulden M, **Krahn M** et al. A cost-utility analysis of common nonsurgical treatments for neck pain. 3rd Annual North American Congress of Epidemiology. Montreal, Canada, June 21-24, 2011 [poster presentation]
50. van der Velde G, Schieir O, Hincapie C, Cote P, Hogg-Johnson S, Paulden M, **Krahn M**. Economic evaluation of the most commonly used non-surgical treatments for neck pain: A cost-tility analysis. International Health Economics Association (iHEA) 8th World Congress, July 10-13, 2011, Toronto Canada (Accepted for oral and poster presentation)
51. Wong W, Bayoumi A, **Krahn M**, Thein HH. Developing a complex agent network model to predict HIV and HCV incidence in Canada. The 3rd International Conference on Infectious Disease Dynamics, Boston, MA, USA 2011 (accepted for poster presentation)
52. Wong W, Bayoumi A, **Krahn M**, Thein HH. Developing a complex agent network model to predict HIV and HCV incidence in Canada. The 33rd Annual Meeting of the Society for Medical Decision Making, October 22-26, 2011, Chicago, IL (accepted for oral presentation)
53. van der Velde G, **Krahn M,** Paulden M, Hincapie C, Schieir O, Cote P, Hogg-Johnson S. Cost-effectiveness of the most commonly used non-surgical treatments for neck pain. 33rd Annual Meeting of the Society for Medical Decision Making, October 22-26, 2011, Chicago IL (accepted for poster presentation).
54. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Disease Burden of Chronic Hepatitis B among Immigrants in Canada. The 33rd Annual Meeting of the Society for Medical Decision Making, October 22-26, 2011, Chicago IL (accepted for poster presentation)
55. Khor S, **Krahn M**, Hodgson D, Bremner K, Luo J, Hoch J. Real World Cost-effecctiveness of Expensive Cancer Drugs: An Example Using Rituximab for Diffuse-Large-B-Cell Lymphoma. CADTH, April 3 - 5, 2011 (Oral presentation)

56. Khor S, **Krahn M**, Hodgson D, Bremner K, Luo J, Hoch J. Real World Cost-effecctiveness of Expensive Cancer Drugs: An Example Using Rituximab for Diffuse-Large-B-Cell Lymphoma. OICR Meeting, Feb 1, 2011 (Poster presentation)
57. Khor S, **Krahn M**, Hodgson D, Bremner K, Luo J, Hoch J. "Real-world cost-effectiveness analysis of cancer drugs; comparative effectivess research using retrospective Canadian registry data before and after drug approval", presented at the International Society for Pharmaceoeconomics and Outcomes Research 16th Annual International Meeting, Baltimore, May 2011
58. G van der Velde, C Hincapié, O Schieir, P Coté, S Hogg-Johnson, M Paulden, M Krahn. Cost-effectiveness of the Most Common Nonsurgical Treatments for Neck Pain. 16th International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Poster Session II, May 24, 2011, Baltimore, United States. *(Accepted for poster presentation February 23, 2011)*
59. Hincapie CA, Schieir O, Cote P, Hogg-Johnson S, Paulden M, **Krahn M**, van der Velde G. A cost-effectiveness analysis of common nonsurgical treatments for neck pain. National Student Conference of the Canadian Society of Epidemiology and Biostatistics, June 19-20, 2011, Montreal Canada (Accepted for oral presentation)
60. Lee L, Hodgson D, Crump M, Khor S, Luo J, **Krahn M**, Bremner K, Hoch J. Impact of Rituximab on Outcomes of Very Elderly Patients With Diffuse Large B-Cell Lymphoma. 11th International Conference on Malignant Lymphoma, Lugano Switzerland, June 15-18, 2011 (Accepted for poster presentation)
61. Ieraci L, **Krahn M**, Paulden M, van der Velde G, Wijeysundera H, Machado M, Witteman W. The cost – effectiveness analysis of five non-invasive cardiac imaging technologies in Ontario. 32nd Annual Meeting of Society for Medical Decision Making Oct 24-27, 2010, Sheraton Centre Toronto, Ontario Canada (*Accepted for poster presentation*).
62. Bornstein M, Franek J, Parthimos M, Nakhai-Pour H, Ieraci L, Paulden M, **Krahn M**, Onetto N, Levin L. Pharmacogenetic testing and evidence-based decision-making in Ontario: The application of Ontario's decision determinants framework to the evaluation of pharmacogenetic tests. 32 Annual Meeting of the Society for Medical Decision Making, October 24-27, 2010, Toronto, ON, Canada (*Accepted for poster presentation*)
63. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. American Association for the Study of Liver Disease (AASLD), October 29-November 2,2011, Boston, MA (accepted for poster presentation)
64. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. The 32nd Annual Meeting of the Society For Medical Decision Making, October 24-27, 2010, Toronto, Ontario Canada (accepted for poster presentation)
65. Wong WWL, Woo G, Heathcote JE, **Krahn M**. Cost effectiveness of screening immigrants for Hepatitis B. Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium, April 18-20, Halifax, NS, Canada (accepted for poster presentation)
66. **Krahn M**. Economic evaluation of preventive strategies for pressure ulcers. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
67. Thein HH, **Krahn M** et. al. Health status utilities in long-term care residents in Ontario. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
68. Chen WD, **Krahn M** et al. Economic evaluation of pressure ulcer preventive strategies for long-term residents in Ontario. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
69. Chen WD, **Krahn M** et al. Economic evalutation of preventive strategies for pressure ulcers: A systematic review. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (panel session)
70. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of Ontario's universal influenza immunization program. iHEA 7th World Congress on Health Economics, July 12-15, 2009 Beijing China (accepted for oral presentation).
71. Woo G, Tomlinson G, Pham B, **Krahn M**. Comparing efficacies of treatments for chronic hepatitis B: A Bayesian mixed treatment comparison meta-analysis. . iHEA 7th World Congress on Health Economics,

July 12-15, 2009 Beijing China (accepted for poster presentation)

72. Wijeysundera H. C, Tomlinson G, Norris CM, Ghali WA, Ko DT, **Krahn M.** Predicting EuroQol EQ-5D Utility Scores from the Seattle Angina Questionnaire in Coronary Artery Disease: A Mapping Algorithm using a Bayesian Framework. 31st Annual Meeting of the Society for Medical Decision Making (SMDM), October 20, 2009 at Hollywood (Los Angeles), California, USA.
73. Pham B, Tomlinson G, Grootendorst P, Witteman W, Wijeysundera H, **Krahn M.** A Systematic Approach to Calibration Analysis of Decision Models for Health Technology Assessment. 31st Annual Meeting of the Society for Medical Decision Making (SMDM), October 18, 2009 at Hollywood (Los Angeles), California, USA.
74. Wijeysundera H, Ko D, Tomlinson G, **Krahn M.** Medical Therapy versus Percutaneous Coronary Intervention in Symptomatic Coronary Artery Disease: Decision Analysis and Economic Evaluation . Canadian Cardiology Congress, October 26th 2009 at Edmonton, Canada
75. Wijeysundera HC, Machado M, Witteman W, Farahati F, van der Velde G, Tu J, Lee DS, Goodman S, Petrella R, O'Flaherty M, Capewell S, **Krahn M.** Reductions in coronary heart disease mortality associated with changes in risk factors in Ontario between 1994 and 2005. Submitted to The Canadian Cardiovascular Congress - CCC, October 24 to 28, 2009 in Edmonton, AB
76. van der Velde G, **Krahn M**, Machado M, Ieraci L, Witteman W, Pham Ba'. The cost-effectiveness of biologic disease modifying anti-rheumatic drugs (DMARDS) compared to conventional DMARDS: A systematic review of economic evaluations. 31st Annual Meeting of the Society for Medical Decision Making (SMDM) Oct 18-21, 2009, California, USA (Accepted for poster presentation)
77. Sander B, **Krahn M**, Bauch C, Fisman D. Impact of mathematical modelling on health policy decision-making in the context of the recent novel Swine-Origin Influenza A Virus (SOIV) outbreak response in Ontario, Canada. 31st Annual Meeting of the Society for Medical Decision Making (SMDM) October 18-21, 2009, California, USA (Accepted for poster presentation)
78. Thein HH, Zagorski BM, Krajden M, **Krahn M.** Population-based estimates of long-term health care costs attributable to hepatitis C. 7th World Congress on Health Economics 12-15 July, 2009, Beijing, China.[Oral]
79. Thein HH, Pham B, **Krahn M**, Wodchis W. Health status utilities and the impact of pressure ulcer in long-term care residents in Ontario. 7th World Congress on Health Economics 12-15 July, 2009, Beijing, China.[Organised session]
80. Machado M, Wijesundera H, Farahati F, Witteman W, van der Velde G, Ieraci, L, Pham B', **Krahn M.** Development of the Ontario Cardiovascular Economic Model. Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium 2009, April 5, 2009, Ottawa, Canada
81. Chen W; Zagorski B; Krajden M; Heathcote J; **Krahn M.** Population-Derived Estimates of Direct Medical Costs Among Late-Stage Hepatitis C Patients with Diabetes Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium 2009, April 5, 2009, Ottawa, Canada
82. Matthew A, Ritvo P, Fleshner N, Lockwood G, Alibhai S, **Krahn M**, Kalnin R, Nesbitt M, Currie K, Santa Mina D, Trachtenberg J: Disease-Specific Distress, Sexual Functioning, and Age in Men After Radical Prostatectomy: An Initial Look at a Complex Picture. (Poster) Canadian Association of Psychosocial Oncology, Survivorship. Transitions & Transformations, Vancouver, British Columbia, April 1-4, 2009.
83. Naglie G, Borrie M, Black S, Beattie B, **Krahn M**, Irvine J, Hogan D, Bergman H, MacKnight C, Patterson C, Byszewski A, Freedman M, Streiner D, Ritvo P, Comrie J, Kowgier M, Tomlinson G. Predictors of quality of life in dementia caregivers. Annual Meeting of the American Geriatrics Society in Chicago, April 20, 2009 (Accepted for Presidential Poster Session)
84. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M.** The cost-effectiveness of Ontario's universal influenza immunization program. Oral presentation, International Health Economics Association 7th World Congress 2009.
85. Woo G, Pham B, Tomlinson G, **Krahn M.** Comparing efficacies of treatements for chronic hepatitis B: A

Bayesian mixed treatment comparison meta-analysis. iHEA 7th World Congress on Health Economics July 12-15, 2009. Beijing, China (Accepted for Poster presentation)

86. Woo G, Pham B, Tomlinson G, **Krahn M**. Comparing efficacies of treatements for chronic hepatitis B: A Bayesian mixed treatment comparison meta-analysis. 44th Annual Meeting of the European Association for the Study of the Liver (EASL), April 22-26, 2009, Copenhagen, Denmark (Accepted for Poster presentation)
87. Chen W, **Krahn M**, et. Al. Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. iHEA 7th World Congress on Health Economics July 12-15, 2009. Beijing, China (Accepted for Oral presentation)
88. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of Ontario's universal influenza immunization program. Poster presentation, Society for Medical Decision Making 30th Annual Meeting, 2008.
89. Van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JC, Cote P, **Krahn M**. Neck pain patients' evaluative scores for their current health state. World Congress on Neck Pain, January 20-22, 2008, Los Angeles, United States.
90. John-Baptiste A, Tomlinson G, Hsu P, Krajden M, Heathcote J, Laporte A, Yoshida E, Anderson F, **Krahn M**. Quality of life following antiviral therapy for chronic hepatitis C virus infection. Poster presentation, 30th Annual Meeting of the Society for Medical Decision Making, Philadelphia, Pennsylvania, USA. October 2008.
91. Thein HH, Pham B, **Krahn M**, Wodchis W. Health status utilities in long-term care residents in Ontario. The 30th Annual Meeting of the Society for Medical Decision Making
92. October 18 - 22, 2008, Philadelphia, Pennsylvania. [Poster]
93. Thein HH, Yi Q, **Krahn M**. Long-term sequelae of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort. 2008 CADTH Symposium 27-29 April 2008, Edmonton, Canada. [Poster]
94. Thein HH, Yi Q, Dore G, **Krahn M**. Natural history of hepatitis C in HIV-infected individuals and the impact of HIV in the era of HAART: a meta-analysis. Can J Gastroenterol 2008;22:(Suppl A), 75A.[Oral]
95. Sander B, Kwong J, Bauch C, Maetzel A, McGeer A, Raboud J, **Krahn M**. The cost-effectiveness of Ontario's universal influenza immunization program. Poster presentation, the European Scientific Working Group on Influenza, 3rd European Influenza Conference 2008.
96. Sander B, **Krahn M**. Influenza vaccine delivery programs: A systematic review. Poster presentation, the European Scientific Working Group on Influenza, 3rd European Influenza Conference 2008.
97. John-Baptiste A, Varenbut M, Lingley M, Teplin D, Daiter J, **Krahn M**. Treatment of hepatitis C infection for current or former substance abusers in a community setting. Oral presentation, 2nd Biennial conference, American Society of Health Economics, Durham, North Carolina, USA. June 2008.
98. John-Baptiste A, **Krahn M**, George Tomlinson. Natural History of Chronic HCV infection obtained through Injection Drug Use: A Bayesian Meta-Analysis. Poster presentation, 2nd Biennial conference, American Society of Health Economics, Durham, North Carolina, USA. June 2008.
99. Wendong Chen, Dinner K, Wong T, Heathcote J, **Krahn M**. Hepatitis C screening among immigrants in Canada. (Podium presentation). Toronto, ISPOR, May 3-7, 2008. Selected as Best Student Podium presentation.
100. Pham B, Machado M, Bombardier C, McMartin K, Bornstein M, Levin L, **Krahn M**. Cost effectiveness of biologics for rheumatoid arthritis: A systematic review (Poster presentation). Toronto, ISPOR, May 3-7, 2008
101. Sander B, **Krahn M**. Influenza vaccine delivery programs: A systematic review (Poster presentation). 2008 CADTH Invitational Symposium, Edmonton, Alberta, April 27-29, 2008.
102. Thein HH, Yi Q, Dore G, **Krahn M**. Natural history of hepatitis C virus infection in HIV-infected individuals in the era of HAART: systematic review and meta-analysis. Hepatology. 2007; 46(4) suppl: 840A. [Poster]

103. Thein H. H., Yi Q, Dore G, **Krahn M**. Natural history of hepatitis C virus infection in HIV-infected individuals in the era of HAART: systematic review and meta-analysis. IAS meeting March 2007.
104. Thein HH, John-Baptiste A, Yi Q, Sander B, Krajden M, **Krahn M**. The Cost-Effectiveness of Nucleic Acid Amplification Testing in the detection of acute hepatitis C virus infection. 6th World Congress on Health Economics 8-11 July, 2007, Copenhagen, Denmark. [Poster]
105. Thein HH, John-Baptiste A, Yi Q, Sander B, Krajden M, **Krahn M**. The Cost-Effectiveness of Nucleic Acid Amplification Testing in the detection of acute hepatitis C virus infection. 2007 CADTH Symposium April 2007, Ottawa, Canada. [Poster]
106. Thein HH, Yi Q, Tomlinson, **Krahn M**. Natural History of Hepatitis C: Systematic Review and Meta-Analysis. National Canadian Research Training Program in Hepatitis C 4th Program Advisory Committee Meeting 2007, Banff, Canada.[Oral]
107. Wendong Chen, **Murray Krahn**, Jenny Healthcote. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. 58th Annual Meeting of the AASLD ,Boston, Massachusetts November 2 - 6, 2007
108. Van der Velde G, Llewellyn-Thomas h, Hogg-Johnson S, Hurwitz E, Cassidey JD, Cote P, **Krahn M**. Neck pain patients' preferences for their current health state. Palma International Forum IX Primary Care Research on Low Back Pain, October 4-6, 2007, Palma de Mllorca, Spain.
109. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JC, Côté P, **Krahn M**. Neck pain patients' evaluative scores for their current health state. Society for Medical Decision Making Annual Meeting, October 20-24, 2007, Pittsburgh, United States.
110. van der Velde G, Llewellyn-Thomas H, Hogg-Johnson S, Hurwitz E, Cassidy JD, Côté P, **Krahn M**. Neck pain patients' evaluative scores for their current health state. 14th Annual Conference of the International Society for Quality of Life Research, October 10-13, 2007, Toronto, Canada. [accepted]
111. van der Velde G, Hogg-Johnson S, Bayoumi A, Cassidy JD, Côté P, Chan S, Subrata P, Hoving JL, Bombardier C, **Krahn M**. A decision analysis of non-invasive neck pain treatments. Society for Medical Decision Making Annual Meeting, October 20-24, 2007, Pittsburgh, United States
112. Chen WD, **Krahn M**, Healthcote J. Prevalence and predictors of obesity among individuals testing positive for hepatitis Cantibody in a multicultural, urban, tertiary care referral clinic. 58th Annual Meeting of the AASLD , Boston, Massachusetts November 2 - 6, 2007.
113. Naglie G., Comrie J., Beattie L., Bergman H., Black S., Borrie M., Byszewski A., Freedman M., Hogan D., Irvine J., **Krahn M**., MacKnight C., Patterson C., Ritvo P., Streiner D., Kowgier M. and Tomlinson G. Patient and Caregiver Quality of Life in Alzheimer's Disease in Relation to Dementia Severity. AGS Annual Meeting, Seattle, May 2007.
114. Sander B, Tomlinson G, **Krahn M**, The Cost-Utility Of Ontario's Universal Influenza Immunization Program, 28th Annual Meeting of the Society for Medical Decision Making, Boston, Massachusetts, October 14-18, 2006.
115. Thein HH, Maruff P, **Krahn M**, Kaldor JM, Koorey D, Brew BJ, Dore GJ. Cognitive and mood effects of antiviral therapy in HCV monoinfected and HIV/HCV coinfected individuals. 2nd Annual Canadian Association for the Study of the Liver Winter Meeting 2006, Toronto, Canada. [Poster]
116. Thein HH, Law M, **Krahn M**, Kaldor JM, Dore GJ. Estimating the impact of antiviral treatment on hepatitis C-related disease burden in Australia. 2nd Annual Canadian Association for the Study of the Liver Winter Meeting 2006, Toronto, Canada. [Poster]
117. Thein HH, Butler T, **Krahn M**, Rawlinson W, Levy M, Kaldor JM, Dore GJ. The effect of hepatitis C virus infection on health-related quality of life in prisoners. 2nd Annual Canadian Association for the Study of the Liver Winter Meeting 2006, Toronto, Canada.
118. Tricco A, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, **Krahn M**, Moher, D. Burden of hepatitis A intervention triggered by infected food-handlers in Canada. CNIC 2006 Conference
119. Anonychuk A, Gilca V, Pham B, Duval B, Bauch C, **Krahn M**. Burden and cost of hepatitis A infection in Canada. 7th Canadian Immunization Conference, Winnipeg Dec 3-6, 2006.
120. Tricco A, Pham B, Duval B, De Serres G, Gilca V, Vrbova L, Anonychuk A, **Krahn M**, Moher D. Published data underestimates the burden of hepatitis A intervention triggered by infected food handlers. 7th Canadian Immunization Conference, Winnipeg Dec 3-6, 2006

121. EM Nelson, G Fraser, AF Connors, MJ Barry, **M Krahn**, MR Conaway, R Bashore, A Wolf, KL Kilbridge, Misunderstanding of Prostate Cancer (CaP) among African American (AA) Men of Lower Socioeconomic Status (Lo-SES), 2006 ASCO Annual Meeting, Atlanta, Georgia, June 2-6, 2006
122. Chen WD, Heathcote J, **Krahn M**. Primary prevention of esophageal variceal bleding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. HTAi 2006 Annual Meeting in Adelaide, Australia July 2-5, 2006.
123. **Krahn M**, Bremner K, Tomlinson G, Alibhai S, Laporte A, Naglie G. Effect of age on preferences for health outcomes in prostate cancer. Philadelphia, ISPOR May 2006
124. Naglie G, Comrie J, Bacher Y, Beattie L, Bergman H, Black S, Borrie M, Byszewski A, Freedman M, Hogan D, Irvine J, **Krahn M**, MacKnight C, Patterson C, Ritvo P, Silberfeld M, Streiner D, Tomlinson G. Quality of Life in Alzheimer's Disease by Severity Level: Preliminary Results from the Canadian Alzheimer's Disease Quality of Life (CADQOL) Study. The Canadian Journal of Geriatrics 2006;9:66.
125. Thein HH, Dore G, Law M, **Krahn M**, Kaldor J. Estimating the impact of antiviral treatment on hepatitis C related disease burden in Australia. 2nd Annual CASL 2006.
126. Thein HH, Maruff P, **Krahn M**, Kaldor J, Koorey D, Brew B, Dore G. Cognitive and mood effects of antiviral therapy in HCV monoinfected and HIV/HCV coinfected individuals. 2nd Annual CASL 2006
127. Chen WD, Heathcote J, **Krahn M**. Primary prevention of esophageal variceal bleeding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. AASLD Program Committee 2006.
128. Bremner K, Bayoumi A, Sherman M, **Krahn M**. Management of solitary 1-2 cm liver nodules in patients with cirrhosis – a decision analysis. 2nd Annual CASL Winter Meeting, Toronto 2006
129. Anonychuk A, Duval B, Bauch C, **Krahn M**, Pham B, Gilca V, Tricco A. Methodological issues in cost effectiveness evaluation of hepatitis A vaccine: A systematic review. 2nd Annual CASL Meeting, Toronto 2006.
130. Anonychuk A, Duval B, Bauch C, **Krahn M**, Pham B, Gilca V, Tricco A. Under-reporting of hepatitis A case notification data in a low endemic country. 2nd Annual CASL Winter Meeting Toronto 2006.
131. Singer L, **Krahn M**, Tullis E, Granton J, Waddell T, Chowdhury N. Disease-specific differences in health-related quality of life in patients referred or listed for lung transplantation. ISHLT 26th Annual Meeting and Scientific Session, Madrid April 2006.
132. Cohen J, Faughnan M, Letarte M, Kennedy M, Vandezande K, **Krahn M**. Cost comparison of genetic and clinical screening in families with HHT. 6th International HHT Conference, Lyon 2005.
133. Anonychuk A, Tricco A, Bauch C, Pham B, **Krahn M**. Methodological issues in cost effectiveness evaluation of hepatitis A vaccine: A systematic review. Society for Medical Decision Making Annual Meeting – San Diego, CA October 2005
134. Anonychuk A, Tricco A, Bauch C, Pham B, **Krahn M**. Methodological issues in cost effectiveness evaluation of hepatitis A vaccine: A systematic review. 56th Annual Meeting of the American Association for the Study of Liver Diseases- San Francisco, CA November 2005
135. Chen WD, **Krahn M**, Wong T, Heathcote J. Body mass index as an independent prognostic factor in chronic hepatitis C infection. Canadian Association for the Study of the Liver Annual Meeting, Banff AB, March 2005
136. Pham B, Tricco A, Bauch C, Chen H, Rao A, **Krahn M**. Use of a catalytic modeling to estimate hepatitis A incidence in a low endemicity country: Implications for modeling immunization policies. 21st. International Conference on Pharmacoepidemilogy and therapeutic risk management: August 2005
137. Tricco A, Pham B, Duval B, Gilca V, **Krahn M**, Moher D. Assessing mass vaccination in outbreaks among infected food handlers: Methodological challenges. 21st International Conference on Pharmacoepidemiology and Therapeutic Risk Management: August 2005
138. Pham B, Tricco A, **Krahn M**. Markov models for cost effectiveness analyses: A framework for assessing

external consistency. 27th annual meeting of the Society for Medical Decision Making, San Francisco, CA October 2005

139. Singer L, **Krahn M,** Gordon CL, Mironyuk L, Tullis DE, Waddell TK, Granton JT. A web-based health-related quality of life (HRQL) assessment tool for lung disease and lung transplant patients. American Thoracic Society Annual Meeting – San Diego May 2005
140. Bauch C, Tricco A, Rao A, Gilca V, Duval B, Pham B, **Krahn M**. Evaluating periodicity of disease transmission prior to cost effectiveness evaluation of immunization programs. Society for Medical Decision Making Annual Meeting, San Francisco, CA October 2005
141. **Krahn M**, Forde N, Mamdani M, Laporte A, Alibhai S, Bremner K, Tomlinson G, Naglie G. Design of longitudinal cost models for the prostate cancer policy model. Society for Medical Decision Making Annual Meeting, October 2005
142. Thein HH, Law M, **Krahn M**, Kaldor JM, Dore GJ. Estimating the impact of antiviral treatment on health burden of HCV in Australia. Student Conference, Sydney, Australia 2005
143. Thein H, Maruff P, **Krahn M**, Kaldor JM, Doorey D, Brew BJ, Dore GJ. The prevalence and correlates of depressive symptoms during pegylated interferon-alpha and ribavirin therapy in HCV monoinfection and HIV-HCV coinfection. 17th Annual Conference of the Australasian Society for HIV Medicine, Hobart, Australia 2005
144. Thein HH, Law M, **Krahn M**, Kaldor JM, Dore GJ. Estimating the impact of antiviral treatment on health burden of HCV in Australia. 17th Annual Conference of the Australasian Society for HIV Medicine, Hobart, Australia 2005
145. Thein H, Maruff P, **Krahn M,** Kaldor JM, Koorey D, Brew BJ, Dore GJ. Health-related quality of life effects of pegylated interferon-alpha and ribavirin therapy in HCV monoinfection and HIV-HCV coinfection. 17th Annual Conference of the Australasian Society for HIV Medicine, Hobart, Australia 2005 (Poster)
146. Thein HH, Law M, **Krahn M**, Kaldor JM, Dore GJ. Estimating the impact of antiviral treatment on health burden of HCV in Australia. Communicable Diseases Control Conference, Sydney, Australia 2005
147. Thein H, Butler T, **Krahn M**, Rawlinson W, Levy M, Kaldor JM, Dore GJ. Health-related quality of life in prisoners with and without chronic HCV infection in Australia. 2nd Prisoners Health Research Symposium, Sydney, Australia 2005
148. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C virus infection from SF-36 scores. NCRTP-HepC PAC Meeting, Banff, Alberta, Canada 2005
149. Ba Pham, **Krahn M**. Assessing the costs of Hepatitis A food related interventions: methodological challenges. 12th International Conference on Pharmacoepidemiology & Therapeutic Risk management, 2005.
150. Thein H, **Krahn M**, Kaldor J, Dore G. Utilities in HCV Infection. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales. Canadian Association for the Study of the Liver Annual Meeting, Banff, March 2005
151. Cotterchio M, Howlett R, Klar N, **Krahn M**, Mai V, McLachlin M, Paszat L, Ritvo P, Stewart D. Ontairo HPV Pilot Study: Practice Implications of Reflex Testing. 22nd International Papillomavirus Conference and Clinical Workshop 2005
152. Sander B, Naglie G, **Krahn M**, Maetzel A. Prevention or Treatment of Influenza in Healthy Adults – A cost-effective option for Society. International Health Economics Association (IHEA) Annual Meeting, Barcelona, July 2005.
153. Hillmer M, **Krahn M,** Naglie G, Hillmer M. Alzheimer's Disease Prescribing Patterns: A National Survey of Canadian Family Physicians. Canadian Geriatrics Society Annual Meeting, August 2005.
154. Cohen J, Faughnan M, Letarte M, Kennedy S, Vandezande K, K**rahn M**. Cost comparison of genetic and clinical screening in families with hereditary hemorrhagc telangiectasia. The American Society of Human

Genetics Annual Meeting, Toronto October 26-30, 2004.

155. Sander B, Naglie G, **Krahn M**, Maetzel A. Prevention or treatment of influenza in healthy adults – a cost-effective option for society? Medical Decision Making. July/August 2004;24(4):438.
156. Chen H, Bauch C, Foty RG, Pham B, **Krahn M**. Use of catalytic modeling to estimate hepatitis A incidence in a low endemicity country: implications for modeling immunization policies. Society for Medical Decision Making Annual Meeting, Atlanta 2004.
157. Pham B, Bauch C, Chen M, Foty R, **Krahn M**. Use of catalytic modeling to estimate hepatitis A incidence in a low endemicity country: implications for modeling immunization policies. 6th Canadian National Immunization Conference, Montreal 2004
158. **Krahn M**. Cost effectiveness of universal hepatitis A vaccination in Canada. Canadian National Immunization Conference, Montreal 2004
159. **Krahn M**, Witkos M, Sanders G, Sugano D, Cantor S. What would make the society and the annual meeting better? a survey of the society for Medical Decision Making Membership. Society for Medical Decision Making Annual Meeting, 2004
160. Bremner K, Bayoumi A, Sherman M, **Krahn M**. Biopsy or resection for single small liver nodules in patients with compensated cirrhosis- a decision analysis. Society for Medical Decision Making, 2004
161. Chen H, Bauch C, Foty R, Pham B, **Krahn M**. Use of Catalytic Modeling to Estimate Hepatitis a Incidence in a Low Endemicity Country: Implications for Modeling Immunization Policies. Society for Medical Decision Making, 2004
162. Cohen J, Faughnan M, Letarte M, Kennedy S, Vandezande K, **Krahn M**. Cost Analysis: Will the new genetic test for HHT save health care dollars?
163. Thein HH, **Krahn M**, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C virus infection from SF-36 scores. 15th Annual conference of the Australasian Society for HIV Medicine, Cairns, Australia 2003
164. Bremner KE, Chong CAKY, Tomlinson G, **Krahn M**. A meta-analysis of utilities for prostate cancer. Medical Decision Making 2003;23(6):544.
165. Bremner KE, **Krahn M**. Do marker states improve the performance of direct utility measures? Medical Decision Making 2003;23(6):544.
166. John-Baptiste A, Cook T, Straus S, Naglie G, Tomlinson G, **Krahn M**. Economic and health consequences of a hyperbaric oxygen cchamber in the international space station. Medical Decision Making 2003;23(6):544.
167. Bremner KE, Tomlinson GA, Naglie G, Ritvo P, Irvine J, **Krahn M**. Prostate cancer patients' preferences for outcomes described by a multiattribute health state classification system for prostate cancer. Medical Decision Making. 22(6): 549, 2002 Nov/Dec
168. Chong CAKY, Naglie IG, **Krahn M**. Numer needed to mislead? NNT does not accurately predict health benefit or efficiency. . Medical Decision Making. 2002 Nov/Dec;22(6): 531
169. John-Baptiste A, Remis RS, Ritvo P, Doria AS, **Krahn M**. Estimating the potential cost-effectiveness of a preventive hepatitis C vaccine. . Medical Decision Making. 2002 Nov/Dec 22(6):534
170. Bremner KE, Tomlinson GA, Naglie G, Ritvo P, Irvine J, **Krahn M**. Predictors of prostate cancer patients' utilities for outcomes described by a multiattribute health state classification system for prostate cancer. Medical Decision Making. 22(6): 559, 2002 Nov/Dec.
171. Tomlinson GA, Bremner KE, Naglie G, Ritvo P, Irvine J, **Krahn M**. Development and validation of a multi-attribute utility function for a multiattribute health state classification system for prostate cancer. Medical Decision Making. 22(6): 560, 2002 Nov/Dec
172. Chong CAKY, Heathcote J, **Krahn M**. "Health State Utilities and Quality of Life in Hepatitis C Patients". 1st Prize, Category 2, Annual Mount Sinai Hospital and University Health Network Department of Medicine Research Competition, June 2002.
173. **Krahn M**., Wang PP & Yi Q. Allocating funds from a national compensation agreement using Markov modeling: The case of the 1986-1990 post-transfusion hepatitis C victims. American College of

Epidemiology Annual Scientific Meeting, Albuquerque, New Mexico, September 22-24, 2002.

174. Cantor SB, Volk RJ, **Krahn M**, Cass AR, Spann SJ. Prostate Cancer Screening Recommendations Based on Couples' Utilities. INFORMS annual meeting, San Antonio Texas, November 2000.
175. Kilbridge KL, Fraser G, **Krahn MD**, Gong DA, Bashore R, Wolf A, Nease RF, Connors AF. Assessing prostate cancer outcomes in rural Africal-American men: are common terms understood? American Society for Clinical Oncology, 2000.
176. Alibhai SMH, Nam R, Naglie G, Trachtenberg J, **Krahn M**. The impact of age, comorbidity, and source of efficacy data on the optimal treatment choice for localized prostate cancer: a decision-analytic view (poster). The Canadian Geriatrics Society Annual Meeting, Edmonton, Canada, October 29, 2000. (senior author)
177. Kilbridge KL, Fraser G, **Krahn M**, Gong DA, Bashore R, Wolf A, Nease R, Connors AF. Assessing prostate cancer outcomes in rural African American men: are common terms understood? Society for Medical Decision Making annual meeting, Cincinnati, September 2000.
178. Alibhai SMH, **Krahn M**, Cohen MM, Fleshner NE, Naglie G. Older Patients Receive Less Aggressive Treatment For Clinically Localized Prostate Cancer. The Canadian Geriatrics Society Annual Meeting, Edmonton, Canada, October 29, 2000.

Poster:

179. Narayanan U, Allan V, **Krahn M**. The optimal mode of delivery of infants with a prenatal diagnosis of spina bifida: a decision analysis . Podium presentation, Society for Medical Decision Making annual meeting, September 2000. (senior author)
180. Alibhai S, Naglie G, **Krahn M**. Surgery, radiotherapy, or watchful waiting for localized prostate cancer: a decision analytic view. Poster presentation, annual student research day, University of Toronto Programme in Clinical Epidemiology and Health Care Research. April 1999. Second prize. (senior author)
181. Narayanan U, Allan V, **Krahn M**. The optimal mode of delivery of infants with a prenatal diagnosis of spina bifida: a decision analysis . Poster presentation, annual student research day, University of Toronto Programme in Clinical Epidemiology and Health Care Research. April 1999. First prize. (senior author)
182. Alibhai S, Naglie G, **Krahn M**. Surgery, radiotherapy, or watchful waiting for localized prostate cancer: a decision analytic view. Poster presentation, student prize for best clinical research project among Geriatrics trainees at the University of Toronto, McMaster University, and The University of Western Ontario, September 1999. (senior author)
183. Sivarajan B, **Krahn M**, Harrison D, Webb G, Siu S. Financial impact of adults with congenital heart disease on health care delivery. Presented at U. of Toronto medical research day, February 1997.
184. Bloomfield D, **Krahn M**, Tannock I. Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone resistant prostate cancer based on a randomized trial with palliative endpoints. Podium presentation, student prize, American Society for Clinical Oncology, May 1997. (senior author)
185. Czaykowski P, **Krahn M**, Oza A. Adjuvant chemotherapy for Stage II colon cancer: clinical and economic effects. Poster presentation, student prize, American Society for Clinical Oncology, May 1997. (senior author)
186. Naglie G, **Krahn M**, Tansey C, Bolley H, Detsky A. Cost-Utility Analysis of Coronary Artery Bypass Surgery Versus Medical Therapy in the Elderly. Podium presentation, Society for Medical Decision Making annual meeting, October 1996.
187. Bloomfield DJ, Tannock IF, **Krahn M**. Should Luteinizing Hormone Releasing Hormone (LHRH) Agonists be continued in the Presence of Hormone Refractory Metastatic Prostate Cancer? A Decision Analysis. Poster presentation, Society for Medical Decision Making annual meeting, October 1996. (senior author)
188. **Krahn M**, Naglie IG, Irvine J, Ritvo P, Trachtenberg J. Patient and expert quality of life ratings in the

construction of an empirically devised domain linked utility instrument for prostate cancer. Poster presentation, Society for Medical Decision Making annual meeting, October 1996.

189. Taylor MC, **Krahn M**, Langer B, Taylor B. The management of liver metastases from colorectal cancer- a decision analysis. Poster presentation, Society for Medical Decision Making annual meeting, Phoenix, October 1995. (senior author)
190. Taylor MC, **Krahn M**, Langer B, Taylor B. "The Management of Liver Metastases from Colorectal Cancer - A Decision Analysis". Poster presentation. The Royal College of Physicians and Surgeons 65th Annual Meeting, Halifax, September, 26-29,1995. (senior author)
191. Naglie G, Tansey C, Bolley H, **Krahn M**, Detsky A. Coronary Bypass Surgery in the Elderly: How Much Does It Cost? Poster presentation. American Geriatrics Society Annual Meeting, 1995.
192. Naglie G, Tansey C, Bolley H, **Krahn M**, Detsky A. An Itemized Costing of Coronary Artery Bypass Surgery in the Elderly. Poster presentation. Royal College of Physicians and Surgeons Annual Meeting, September 1995.
193. **Krahn M**, Detsky AS. Costs and cost effectiveness of British Columbia's grade six hepatitis B vaccination program. Podium presentation. Society for Medical Decision Making annual meeting, October 1995.
194. **Krahn M**, Mahoney J, Eckman M, Detsky AS. PSA Screening for prostate cancer: a decision analytic perspective. Poster presentation, American Urological Association annual meeting, September 1993.
195. **Krahn M**, Detsky AS. Universal Vaccination for Hepatitis B in North America. Podium presentation, American Federation for Clinical Research Annual Meeting, Seattle, May 1991.
196. **Krahn M**, Naylor CD, Basinski AS, Detsky AS. Quality of Life and Cholesterol Policy. Podium presentation, American Federation for Clinical Research Annual Meeting, Washington D.C. won Henry Christian Memorial Award for best abstract in Clinical Epidemiology, May 1990.
197. **Krahn M**. Thyrotoxic periodic paralysis," Clinical Vignette, College of Physicians and Surgeons Annual Meeting, 1986.

LIST OF COURSES TAUGHT SINCE DATE OF LAST PROMOTION

2011 – Present
Develop, coordinate and teach for the Health Technology Institute

2010- Present
PHM 1128 Introduction to Models and Methods of Research in Clinical, Social and Administrative Pharmacy
Annual lecture in Technology assessment models and methods.

2005 - Present
HAD 5312H Decision Modeling for Clinical Policy and Economic Evaluation

2003 - 2005
HAD 7002 Decision Modeling for Clinical Policy and Economic Evaluation
Developed the course, coordinate the course, teach 4 sessions, mark assignments, tutor 2-4 students per year.

1998 - 2004
CHL 5760. Introduction to Health Economics. Annual lecture in decision analysis.

1993-2004
HAD 5304F Medical Decision and Cost Effectiveness Analysis. Course co-coordinator 1993-2000. Prepared course materials for two sessions, co-wrote the "Primer" series which serves as the course text. Teach 2 sessions: Introduction to Tree age, and "Sensitivity Analysis". Tutor 4-6 students over the entire half-course, review and mark final oral and written presentations for tutored students.

1993-2000
CLB 1407: From Bench to Bedside (Introduction to Clinical Epidemiology and Health Services Research for Laboratory Scientists). Course coordinator. Designed and prepared course materials, taught 7-8 sessions x 2 hrs each year.

1993-1998
HAD 5301 Introduction to Clinical Epidemiology and Health Care Research, taught 1-3 sessions x 2.5 hrs each year. Prepared course materials for "Decision Analysis" Module.

STUDENTS SUPERVISED

Postdoctoral Fellows

1. Frieda Daniels, 2013. Institute of Health Policy, Management and Evaluation, University of Toronto.
2. Petros Pechlivanglou, 2012 - , Institute of Health Policy, Management and Evaluation, University of Toronto.
3. Hong Anh Tu (co-supervisor), 2011 - , Institute of Health Policy, Management and Evaluation, University of Toronto.
4. Gabrielle van der Velde (primary supervisor), 2005-2008. Health Policy, Management, and Evaluation,University of Toronto.
5. William Wong (supervisor) University of Toronto, 2010 - 2012
6. Claire Oliveira (supervisor) University of Toronto, 2010 -
7. Hla Hla Thein (supervisor) University of New South Wales, 2007- 2009.
8. Tony Dowling, (co-supervisor) (Melbourne, Australia). Department: Clinical Epidemiology, 1999. Topic: Using PSA as a marker of disease progression in advanced prostate cancer.
9. Wendy Chiu, (secondary supervisor), McGill University, 1999- Topic: Age as a predictor of treatment choice in elective aortic aneurysm repair. A decision analytic view.
10. Ellen Mozurkewich, (co-supervisor), University of Michigan, 1999. Topic: Alternate strategies for threatened pre-term delivery: a decision analysis.
11. Rob Klassen, (secondary supervisor), University of Toronto, 1998-1999, Topic: Initial bone-marrow aspiration in childhood ITP: a decision analysis.
12. Jane Collier, (primary supervisor) (Cambridge University), 1997-8. Topic: Cost-utility analysis of screening HbsAg carriers.
13. David Bloomfield, (co-supervisor) (University of London), 1997-8, Topic: Economic evaluation of mitoxantrone and prednisone for hormone refractory prostate cancer.

PhD Students

1. Aysegul Erman. Faculty of Pharmacy, University of Toronto, 2013
2. Arlene Nugent (co-supervisor), The use of quality of life data in health policy decision making, Institute of Health Policy, Management and Evaluation, University of Toronto, 2013 -
3. Yeesha Poon (primary supervisor), Cost effectiveness analysis in prostate cancer, Faculty of Pharmacy, University of Toronto, 2011 - present
4. Mary-Ellen Hogan, (co-supervisor), Cost of chronic pain, University of Toronto, 2011 - present
5. Amy Tawfik (supervisor), Understanding the real world functioning of the drug reimbursement in Canada; from model building to listing decision, Faculty of Pharmacy, University of Toronto, 2011- present
6. Nader Kabboul (supervisor), The cost-effectiveness of Cardiac Rehabilitaion treatment strategies in patients with Coronary Faculty of Pharmacy, University of Toronto 2010 –
7. Natasha Nanwa (primary supervisor), Estimating the economic burden of infectious diseases using health administrative data, Graduate Department of Pharmaceutical Sciences, University of Toronto, 2010 –
8. Brian Chan (primary supervisor), The Economic Burden of Chronic Ulcers, Graduate Department of Pharmaceutical Sciences, University of Toronto, 2010 –
9. Mina Tadrous (committee member), Graduate Department of Pharmaceutical Sciences, University of Toronto, 2010 - present
10. Milica Nikitovic (committee member), Graduate Department of Pharmaceutical Sciences,

University of Toronto, 2010 - present
11. Maryse Bouchard (committee member), University of Toronto, 2010 - present
12. Harindra Wijeysundera (Supervisor), Clinician-Scientist Program, Department of Medicine, U of T, 2007-2010
13. Gloria Woo (primary supervisor), Faculty of Pharmacy, University of Toronto, 2005- 2010
14. Ba Pham (co-supervisor), Health Policy, Management, and Evaluation, University of Toronto, 2005-2011
15. Wendong Chen (primary supervisor), HPME, NCRTP-Hep C, 2005 - 2010
16. Holly Witteman (committee member) Mechanical and Industrial Engineering, University of Toronto, 2003-2010
17. Beate Sander (primary supervisor), Health Policy, Management, and Evaluation, 2003-2011
18. Ava John-Baptiste (primary supervisor) Health Policy, Management, and Evaluation. Costs, quality of life, and cost effectiveness of treating injection drug users for HCV infection. 2002-2009
19. Andreas Maetzel (thesis committee), 1999-2002. Institute of Medical Science. Topic: Cost effectiveness of cyclo-oxygenase 2 inhibitors: a cost effectiveness analysis.
20. HeYu (co-supervisor). PSA as a predictor of prognosis in breast and prostate cancer. PhD, Department of Clinical Biochemistry, 1995.

MSc / MHSc Students

1. Troy Francis (Co-supervisor), Leslie Dan Faculty of Pharmacy, University of Toronto, 2014 - present
2. Austin Nam (Co-supervisor), Health Services Research MSc program, University of Toronto, 2013 - present
3. Nathan Perlis (primary supervisor), Quality of life and bladder cancer, University of Toronto, 2011 - 2013
4. Bridget Maturi (supervisor), the cost effectiveness of intermittent versus continuous androgen deprivation therapy in advanced prostate cancer, University of Toronto, 2009 – present
5. Amy Tawfik (supervisor), 2009 - 2011
6. Matt Witkos (primary supervisor). MSc 2003, Department of Health Policy, Management, and Evaluation. Predictors of antiviral therapy in a cohort of post transfusion HCV patients.
7. Gabrielle van der Velde (primary supervisor), 2001- 2005. Utility assessment and decision modeling in patients with acute and chronic neck pain. MSc in clinical epidemiology- transferring to PhD
8. Mark Taylor (primary supervisor), 1997-99. Department: Clinical Epidemiology. Topic: Costs of liver transplantation: effects of clinical diagnosis, disease severity, and surgical complications. MSc in Clinical Epidemiology, completed in 1999.
9. Rob Nam (primary supervisor), 1998-2000. Department: Clinical Epidemiology. Topic: Genetic predictors of metastatic disease progression in prostate cancer: a case control study. MSc in Clinical Epidemiology completed in 2000.
10. Katina Tzanetos (primary supervisor), 2000-4. Department: Clinical Epidemiology. Topic: Characteristics of the Great Attending Physician.
11. Derek Wilke (thesis committee), 2000-2005. Department of Clinical Epidemiology. Topic: Probability tradeoffs in patients considering adjuvant hormonal therapy for localized prostate cancer.
12. Unni Narayanan (thesis committee), 2000-. Department of Clinical Epidemiology. Topic: Spontaneous vaginal delivery versus elective cesarian section in spina bifida infants: a decision analysis. In progress.
13. Yelena Potylitsina (primary supervisor), 2000-. MHSc Degree, Department of Laboratory Medicine

and Pathobiology. Topic: Meta-analysis of natural history studies in HCV infection. In progress.

14. Piotr Czaykowski (primary supervisor), 1997-1998. Department: Clinical Epidemiology. Topic: Cost-utility of adjuvant chemotherapy for colorectal cancer. Degree not completed.
15. Vanita Jassal (thesis committee), 1998-1999. Department: Clinical Epidemiology. Topic: Renal transplant in the elderly: a decision analysis. MSc completed in 1999.
16. Phil McFarland (thesis committee), 1999- . Department: Clinical Epidemiology. Topic: Cost-effectiveness of home nocturnal hemodialysis. In progress.
17. Sergio Rueda (thesis committee), 1999-2000. Institute of Medical Science. Topic: Adequacy of three quality of life measures for dementia: patient and family input. MSc completed in 1999.
18. Shabbir Alibhai (thesis committee), 1999- Department of Clinical Epidemiology. Topic: Age and co-morbidity as predictors of treatment choice for patients with localized prostate cancer. Completed 2002.

Undergraduate

1. Judy Chou, 2009
2. Man Wah Yeung, 2008 – 2009
3. Victoria Leung, 2009
4. Kevin Schwartz (co-supervisor), 2004.
5. Chris Chong, 2002-2003. Utilities in hepatitis C patients.
6. Jamil Asaria (primary supervisor), 1999. National survey of practice patterns among urologists and radiation oncologists.
7. Anil Srivastava (primary supervisor), 1995, Topic: Utilities for impotence: self health and standardized health states.

Thesis Committee

1. Rebecca Waldie
2. Kavisha Jayasundera
3. Mallory Tsao
4. Aysegul Erman
5. Mina Tadrous
6. Dolly Han
7. Sojung Lee
8. Chang Ho Lee
9. Jamie Lineen
10. Stephanie Choi

This is Exhibit "C" referred to in the Affidavit of Murray Krahn sworn before me, this 16th day of March, 2015

A COMMISSIONER FOR TAKING AFFIDAVITS

Wendong Chen, MD, PhD

Independent Health Economist, Normin Health

Assistant Professor (status only),
Division of Social and Administrative Pharmacy
Leslie Dan Faculty of Pharmacy, University of Toronto

Investigator, Toronto Health Economics and Technology Assessment Collaborative (THETA),
University of Toronto

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Phone (416) 604-1287; Mobile (647) 289-3918
wendong.chen@normin.ca

A. DATE PREPARED: November 4, 2014

B. BIOGRAPHICAL INFORMATION

1. EDUCATION

1991-1996	Bachelor of Medicine Beijing University, Beijing, China
2000	Introduction to Product Management, IMS HEALTH, Shanghai, China
2002	Evidence-based Clinical Practice and Health Technology Assessment, Copenhagen Trial Unit, University of Copenhagen, Copenhagen, Denmark.
2005-2009	Research Trainee National Canadian Research Training Program in Hepatitis C, Toronto, Canada
2010	Health Care Management in United Kingdom: the application of National Institute for Health and Clinical Excellence (NICE). London, UK.
2005-2010	Doctor of Philosophy Department of Health Policy, Management and Evaluation, University of Toronto Thesis: Chronic Hepatitis C infection among Immigrants Living in Canada: Natural History, Disease Burden, and Cost-effectiveness of Screening Primary supervisor: Dr. Murray Krahn; Co-supervisor: Dr. Jenny Heathcote

2. EMPLOYMENT

1996-1999	Research Associate, Department of Pharmacology, Xuanwu Hospital, Capital University of Medical Sciences, Beijing, China
1999-2001	Product Manager, Division of Marketing, Merck Beijing Representative Office, Beijing, China.
2001-2003	Cochrane Systematic Reviewer, The Cochrane Heapto-Biliary Review Group, University of Copenhagen, Copenhagen, Denmark.
2003-2004	Research Associate, Department of Medicine, University Health Network,

	Toronto, Canada.
2010-2012	Senior Scientific Associate, Department of Medicine, Toronto General Hospital, University Health Network, Toronto, Canada
2012-Present	Independent Health Economist, Normin Health, Toronto, Canada

3. ACADEMIC APPOINTMENT

2010-present	Assistant Professor, Division of Social and Administrative Pharmacy Leslie Dan Faculty of Pharmacy, University of Toronto
2010-present	Investigator, Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto
2010-present	Adjunct Scientist, China National Health Development Research Center, Ministry of Health of People's Republic of China

4. TEACHING EXPERIENCE

2005	University of Toronto: Summer student supervisor. Summer student: Terence Wong, undergraduate at University of Toronto Project: The relationship between body mass index and chronic hepatitis C
2006	University of Toronto: Summer student supervisor. Summer student: Ayaaz Sachedina, undergraduate at University of Western Ontario. Project: The prevalence of comorbidities in patients with chronic hepatitis C
2007	University of Toronto: Teaching Assistant. Course name: Canadian Health Policy and Health Economic Evaluation. Faculty of Pharmacy, University of Toronto.
2008	University of Toronto: Tutorial leader. Course name: Canadian Health Policy and Health Economic Evaluation. Faculty of Pharmacy, University of Toronto.
2009	University of Toronto: Summer student supervisor. Summer student: Mo Yu, undergraduate at University of Toronto Project: Direct medical costs associated with patients with chronic hepatitis C.
2011	Core Faculty for 2011 HTA Summer Institute, Toronto, Canada
2012	Core Faculty for 2012 HTA Summer Institute, Toronto, Canada
2012	Core Faculty for 2012 HTA Workshop for Decision Makers in Beijing, China
2012	Academic Secretary and Core Faculty for 2012 Canadian Liver Foundation International Clinical Research Program in Hepatology
2012 to 2014	Course lecturer for pharmacoeconomics (PHM213H1)
2013	Summer student supervisor for Weifang Dai
2013	Supervisor for visiting fellows (Drs. Huaying Zhou and Zhengping Xiong)

2013	Lecturer for cost-effectiveness analysis for economic evaluation course at HPME
2013 to 2014	4th undergraduate research course supervisor for Irfan Nagi
2013 to 2014	Neda Ebrahimi's PhD committee member
2014	Lecturer for cost-effectiveness analysis for graduate research methods course at pharmacy, U of T

5. HONOURS AND AWARDS

2005	Doctoral Award, National Canadian Research Training Program in Hepatitis C
2006	Province of Ontario Graduate Award
2006	Second Prize for Oral Presentation, Toronto Western Hospital Research Day
2007	Province of Ontario Graduate Award
2007	Graduate Award, Canadian Liver Foundation
2007	Trainee Travel Award, Canadian Agency for Drugs and Technologies in Health 2007 Symposium
2008	Best Student Podium Presentation, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 13th Annual International Meeting
2008	Trainee Travel Award, Canadian Agency for Drugs and Technologies in Health 2008 Symposium
2009	Trainee Travel Award, Canadian Agency for Drugs and Technologies in Health 2009 Symposium
2011	Poster Finalist Award, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 16th Annual International Meeting in Baltimore, USA.

6. PROFESSIONAL AFFILIATIONS AND ACTIVITIES

A. PROFESSIONAL MEMBERSHIPS

2005-present	Canadian Association for the Study of the Liver
2005-present	Society for Medical Decision Making
2005-present	International Society for Pharmacoeconomics and Outcomes Research
2005-present	International Health Economics Association

B. RESEARCH AWARDS

Salary support

2005-2009	Doctoral Award National Canadian Research Training in Hepatitis C

$88,000

2006 Province of Ontario Graduate Award
Government of Ontario
$15,000

2007 Province of Ontario Graduate Award
Government of Ontario
$15,000

2008-2010 Graduate Award
Canadian Liver Foundation
$40,000

Approved operating grants

2009 Patterns of care and direct medical costs associated with type 2 diabetes in China and Canada: comparisons between a developing country and a developed country (Letter of Intent).
Funding agency: Canadian Institutes of Health Research
Funding approved: $10,000
Principal Investigator: Murray Krahn
Co-Investigators: **Wendong Chen**, Baiju Shah, Zhengzhong Zhang, Kun Zhao

2011-2012 The burden of chronic hepatitis C under the patterns of current care in British Columbia, Canada.
Funding agency: Canadian Liver Foundation
Funding approved: $375,275
Principal Investigator: Murray Krahn
Co-Investigators: **Wendong Chen**, Mel Krajden.

2012 Comparing microsimulation model versus Markov model in assessing the cost-effectiveness of low-dose computed tomography for lung cancer screening in heavy smokers.
Funding agency: Canadian Partnership Against Cancer
Funding approved: $15,000
Principal Investigator: **Wendong Chen**
Co-Investigators: Murray Krahn

2012 Cost-effectiveness of antiviral therapy for chronic hepatitis B: a systematic review
Funding source: BMS unrestricted research grant
Funding approved: $60,000
Principal Investigator: **Wendong Chen**

2013 Tumor response, toxicity, and hospital costs associated with patients with advanced non-squamous non-small cell lung cancer
Funding source: Eli Lilly unrestricted health outcomes research grant
Funding approved: $160,000
Principal Investigator: **Wendong Chen**

2013 Clinical effectiveness and hospital costs associated with vancomycin and linezolid for treating hospitalized-acquired pneumonia in a tertiary hospital setting: a retrospective cohort study
Funding source: Eli Lilly unrestricted health outcomes research grant
Funding approved: $46,000
Principal Investigator: **Wendong Chen**

2013 The fifth revision plan for the long-term predictions in a hepatitis C compensation cohort in Canada.
Funding source: The hepatitis C compensation settlement trust fund
Funding approved: $200,000
Principal Investigator: Murray Krahn; Co-principal investigator: **Wendong Chen**

2014 Clinical effectiveness, toxicity, and cost-effectiveness of bortezomib for multiple myeloma: a systematic review
Funding source: J & J unrestricted research grant
Funding approved: $50,000
Principal Investigator: **Wendong Chen**

C. PUBLICATIONS

Peer-Reviewed

1. Yan Wang, Jianhua Chen, Shengqi Wu, Chenping Hu, Xiaoling Li, Yuqin Wang, Yicheng Yang, Narayan Rajan, Yun Chen, Yi Chen, Zhuanzhuan Luo and **Wendong Chen**. Clinical Effectiveness and Clinical Toxicity Associated with Platinum-Based Doublets in the First-Line Setting for Advanced Non-Squamous Non-Small Cell Lung Cancer in Chinese Patients: A Retrospective Cohort Study. BMC Cancer 2014; 14:937.
2. Yuanlin Song, Yicheng Yang, **Wendong Chen,** Wei Liu, Kai Wang, Xuehai Li, Ke Wang, Manny Papadimitropoulos, William Montgomery. Clinical response and hospital costs associated with the empirical use of vancomycin and linezolid for hospital-acquired pneumonia in a Chinese tertiary care hospital: a retrospective cohort study. Journal of ClinicoEconomics and Outcomes Research 2014;6: 451-461.
3. Chengping Hu, Yan Wang, Jianhua Chen, Shengqi Wu, Xiaoling Li, Yuqin Wang, Yicheng Yang, Narayan Rajan, Manny Papadimitropoulos, Qiong Xiao, Huan Zhan, **Wendong Chen**. Tumor Response and Clinical Toxicity Associated with Second-Line Chemotherapy Regimens for Advanced Non-Squamous Non-Small Cell Lung Cancer: A Retrospective Cohort Study. Thoracic Cancer 2014;5(5):365-376.
4. Krahn MD, Bremner KE, Zagorski B, Alibhai SM, **Chen W**, Tomlinson G, Mitsakakis N, Naglie G.Health Care Costs for State Transition Models in Prostate Cancer. Med Decis Making. 2013 Jul 26.
5. **Chen W.** Economic burden of liver cancer and economic evidence of interventions preventing liver cancer in low or middle-income countries. Disease Control Priorities, Third Edition (2014). World Bank.
6. **Chen W**, Tomlinson G, Krahn M, Heathcote J. Immigrant Patients with Advanced Fibrosis and Hepatitis C Infection have a higher risk of hepatocellular carcinoma. Journal of viral hepatitis 2012; 19(8): 574-80.
7. Pham B, Stern A, **Chen W**, et al. Preventing pressure ulcers in long-term care: a cost-

effectiveness analysis. Arch Intern Med. 2011;171(20):1839-47.
8. **Chen W**, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. J Hepatol. 2008;49(5):711-7.
9. Veldt BJ, **Chen W**, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, de Knegt RJ, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology 2008;47(6):1856-62.
10. Siersma V, Als-Nielsen B, **Chen W**, Hilden J, Gluud LL, Gluud C. Multivariable modelling for meta-epidemiological assessment of the association between trial quality and treatment effects estimated in randomized clinical trials. Stat Med. 2007;26(14):2745-58.
11. **Chen W**, Krahn M. Review: Ribavirin is not better than placebo in chronic hepatitis C infection. ACP J Club. 2006. 145(2):47.
12. Klingenberg SL, **Chen W**. D-penicillamine for primary sclerosing cholangitis. The Cochrane Library. 2006. Issue 1.
13. **Chen W**, Gluud C. Hepatitis B vaccine for healthcare workers. The Cochrane Library. 2005. Issue 4.
14. **Chen W**, Gluud C. Bile acids for liver transplanted patients. The Cochrane Library. 2005. Issue 3.
15. **Chen W**, Gluud C. Glucocorticosteroids for primary sclerosing cholangitis. The Cochrane Library. 2004. Issue 3.
16. Als-Nielsen B, **Chen W**, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA.2003.290(7):921-8.
17. **Chen W**, Liu J, Gluud C.Bile acids for viral hepatitis.The Cochrane Library.2003.Issue 2.
18. **Chen W**, Gluud C. Bile acids for primary sclerosing cholangitis. The Cochrane Library. 2003. Issue 2.

Abstracts-Refereed

1. **Chen W**, Tomlinson G, Krahn M, Heathcote J. High Risk of Hepatocellular Carcinoma Associated with Immigrant Patients with Advanced Fibrosis and Hepatitis C Infection from a Tertiary Referral Clinic in Toronto, Canada. HEPATOLOGY. 2009; 50(4) suppl: 673A.
2. **Chen W**, Tomlinson G, Heathcote EJ, Krahn M. Disease burden and lifetime direct medical costs of chronic hepatitis C infection among immigrants living in Canada. HEPATOLOGY 2009;50(4) suppl: 658A.
3. **Chen W**, Zagorski, M. Krajden, Heathcote EJ, Krahn M. Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. HEPATOLOGY 2008;47 (4): 120A.
4. **Chen W**, Dinner K, Wong T, et al. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. HEPATOLOGY 2007;46 (4): 891A.
5. **Chen W**, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. HEPATOLOGY. 2007;46 (4): 632A.
6. **Chen W**, Cope S, Watkins J, Heathcote J, Krahn M. Primary prevention of esophageal variceal bleeding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. Gastroenterology. 2006.130 (suppl 2): A811.
7. **Chen W**, Wong T, Heathcote J, Krahn M. Prevalence and predictors of high body mass index among native born and immigrant patients with chronic hepatitis C in Canada. Gastroenterology. 2006.130 (suppl 2):A780.
8 **Chen W**, Nikolova D, Frederiksen SL, Gluud C. Beta-blockers for the prevention of first variceal

bleeding in cirrhotic patients with oesophageal varices. [A Cochrane systematic review]. Journal of Hepatology. 2004;40(S1):67.

9 **Chen W**, Gluud C. Bile acids for primary sclerosing cholangitis [A Cochrane systematic review]. Journal of Hepatology. 2003;38(S2):205.

D. PRESENTATIONS AND SPECIAL LECTURES

Invited lectures

August 2010	How to apply Markov model to estimate the disease burden. China National Health Development Research Center. Beijing, China.
August 2010	How to apply Markov model to estimate the disease burden. Chinese Center for Disease Control and Prevention. Beijing, China.
November 2010	Cost-Effectiveness of Epidermal Growth Factor Receptor Gene Mutation Testing For Patients with Advanced Non-Small Cell Lung Cancer Living in Ontario. Cancer Care Ontario. Toronto, Canada.
March 2011	Cost-Effectiveness of Epidermal Growth Factor Receptor Gene Mutation Testing For Patients with Advanced Non-Small Cell Lung Cancer Living in Ontario. The third teaching hospital of Hebei Medical University, Shijiazhuang, China.
November 2011	Chronic hepatitis C and immigrants living in Canada. Canadian Liver Foundation. Toronto, Canada.
May 2012	Applications of disease mathematical model in healthcare: from clinical research to health policy making • The second teaching hospital of Central-South University, Changsha, China • The third teaching hospital of Central-South University, Changsha, China • Hunan Provincial People Hospital, Changsha, Hunan, China • Hunan Cancer Hospital, Changsha, China • Hunan Children Hospital, Changsha, China • The second teaching hospital of Sichuan University, Chengdu, China • Beijing Cancer Hospital, Beijing University, Beijing, China • Xuanwu Hospital, Capital University of Medical Sciences, Beijing, China
August 2012	Chronic hepatitis C among immigrants living in Canada: natural history, disease burden, and cost-effectiveness of screening. Leslie Dan Faculty of Pharmacy, University of Toronto

Oral presentations at meetings

March 2003	A lecture on systematic review of bile acids for liver diseases. The 15th Gastroenterology International Club Meeting, Naples, Italy.
July 2003	A lecture on systematic review of bile acids for liver diseases. The 38th annual meeting of European Association for the Study of the Liver, Geneva, Switzerland.
April 2004	A lecture on systematic review of bile acids for liver transplanted patients. The 39th annual meeting of European Association for the Study of the Liver, Berlin,

	Germany.
April 2004	A lecture on systematic review of beta-blockers for the first variceal bleeding in cirrhotic patients. The 39th annual meeting of European Association for the Study of the Liver, Berlin, Germany. April 16, 2004.
November 2004	A lecture on systematic review of bile acids for variceal rebleeding in cirrhotic patients. The 55th annual meeting of American Association for the Study of Liver Diseases, Boston, USA.
April 2006	Prevalence and predictors of high body mass index among native born and immigrant patients with chronic hepatitis C in Canada. The 3nd annual meeting of Canadian Association for the Study of the Liver, Toronto, Canada.
March 2007	A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. The 2nd annual meeting of Canadian Association for the Study of the Liver, Banff, Canada.
May 2008	A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. The 13th annual meeting of International Society of Pharmcoeconomics and Outcome Research in Toronto, Canada.
October 2008	Health economic evaluation of pressure ulcer prevention options in long-term care setting across Ontario, Canada. The 30th annual meeting of the Society for Medical Decision Making in Philadelphia, USA.
November 2008	Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. The 59th annual liver meeting of American Association for the Study of Liver Diseases. San Francisco, USA.
Februrary 2009	Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. 4th Annual meeting of Canadian Association for the Study of the Liver. Banff, Canada.
March 2009	Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. The Sheila Sherlock Research Day. Toronto, Canada.
March 2009	High risk of hepatocellular carcinoma associated with immigrant patients with advanced fibrosis and hepatitis C infection from a tertiary referral clinic in Toronto, Canada. The Sheila Sherlock Research Day. Toronto, Canada.
May 2009	Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. Toronto Western Hospital Research Day. Toronto, Canada.
July 2009	Population-derived estimates of direct medical costs among late-stage hepatitis C patients with diabetes. The 7th World Congress of Health Economics, International Health Economics Association, Beijing China.
July 2009	Health economic evaluation of pressure ulcer prevention options in long-term care setting across Ontario, Canada. The 7th World Congress of Health Economics, International Health Economics Association, Beijing China.
October 2009	Diseases burden and lifetime direct medical costs of chronic hepatitis C among immigrants living in Canada. The 31th annual meeting of the Society for Medical Decision Making in Los Angeles, USA.
April 2011	Cost-effectiveness of EGFR gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. 2011 CADTH Symposium. Vancouver, Canada.
June 2011	Cost-effectiveness of EGFR gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. HTAi 2011 Annual Conference. Rio de Joneiro, Brazil.
October 2011	Cost-effectiveness of EGFR gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. The 33th annual meeting of the Society for

	Medical Decision Making in Chicago, USA.
September 2013	Cost-effectiveness of image-based methods for HCC screening: a systematic review. The 7th International Liver Cancer Association Annual Meeting in Washington DC

Post presentations at meetings

May 2003	**Chen W**, Gluud C. Bile acids for primary sclerosing cholangitis [A Cochrane systematic review]. The 39th annual meeting of European Association for the Study of the Liver, Berlin, Germany.
April 2004	**Chen W**, Nikolova D, Frèderiksen SL, Gluud C. Beta-blockers for the prevention of first variceal bleeding in cirrhotic patients with oesophageal varices. [A Cochrane systematic review]. The 38th annual meeting of European Association for the Study of the Liver, Geneva, Switzerland.
May 2006	**Chen W**, Cope S, Watkins J, Heathcote J, Krahn M. Primary prevention of esophageal variceal bleeding among cirrhotic patients with hepatitis C and grade 2 to 3 esophageal varices: a cost-utility analysis. Digestive Diseases Week. Los Angeles, USA
May 2006	**Chen W**, Wong T, Heathcote J, Krahn M. Prevalence and predictors of high body mass index among native born and immigrant patients with chronic hepatitis C in Canada. Digestive Diseases Week. Los Angeles, USA
October 2007	**Chen W**, Dinner K, Wong T, et al. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. The 29th annual meeting of the Society for Medical Decision Making in Pittsburg, USA.
November 2007	**Chen W**, Dinner K, Wong T, et al. A cost-effectiveness analysis of hepatitis C screening among immigrants in Canada. The 58th annual meeting of American Association for the Study of Liver Diseases in Boston, USA.
November 2007	**Chen W**, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. The 58th annual meeting of American Association for the Study of Liver Diseases in Boston, USA.
November 2009	**Chen W**, Tomlinson G, Krahn M, Heathcote J. High Risk of Hepatocellular Carcinoma Associated with Immigrant Patients with Advanced Fibrosis and Hepatitis C Infection from a Tertiary Referral Clinic in Toronto, Canada. The 60th annual meeting of American Association for the Study of Liver Diseases. Boston, USA
November 2009	**Chen W**, Tomlinson G, Heathcote EJ, Krahn M. Disease burden and lifetime direct medical costs of chronic hepatitis C infection among immigrants living in Canada. The 60th annual meeting of American Association for the Study of Liver Diseases in Boston, USA.
October 2010	Pharmcogenetic testing and evidence-based decision making in Ontario: The application of Ontario's decision determinants framework to the evaluation of pharmacogenetic tests. The 32th annual meeting of the Society for Medical Decision Making in Toronto, Canada.
May 2011	**Chen W**, Ellis P, Krahn M. Cost-effectiveness of EGFR gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 16th Annual International Meeting in Baltimore, USA.
July 2011	**Chen W**, Ellis P, Krahn M. Cost-effectiveness of EGFR gene mutation testing for patients with advanced non-small cell lung cancer living in Ontario. The 8th World Congress of Health Economics, International Health Economics Association in Toronto, Canada.

October 2013 Chenping Hu, Yan Wang, Jianhua Chen, Shengqi Wu, Xiaoling Li, Yuqin Wang, Yicheng Yang, Narayan Rajan, Manny papadimitropoulos, Qiong Xiao, **Wendong Chen.** Tumor response, toxicity, and hospital costs associated with chemotherapy regimens in second-line setting for advanced non-squamous non-small cell lung cancer. The 15th World Lung Cancer Conference. Sydney, Australia.

October 2013 Huaying Zhou, Weifang Dai, Guozhong Gong, **Wendong Chen**. PREDICTORS FOR DOSE REDUCTION CAUSED BY HEMATOLOGICAL ADVERSE EVENTS IN PATIENTS WITH ADVANCED FIBROSIS RECEIVING PEGYLATED INTERFERON PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C: A SYSTEMATIC REVIEW AND META-REGRESSION ANALYSIS. The 35th Annual Meeting of the Society for Medical Decision Making. Boston, USA.

November 2013 Zhengpin Xiong, **Wendong Chen**, Morris Sherman. Cost-effectiveness of image-based methods for HCC screening: a systematic review. The 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013. Washington DC. USA.

September 2014
- Hospital costs associated with platinum-based doublets in the first-line setting for advanced non-squamous non-small cell lung cancer in China: a retrospective cohort study
- Cost-effectiveness of antiviral therapy for chronic hepatitis B: a systematic review
- Clinical response and hospital costs associated with the empirical use of vancomycin and linezolid for hospital-acquired pneumonia in a Chinese tertiary care hospital: a retrospective cohort study

The 6th ISPOR Asia-Pacific conference in Beijing, China

E. MEDIA REPORTS

March 6, 2012 Interviewed by OMNI TV on the high risk of liver cancer among immigrants with chronic hepatitis C.

March 7, 2012 Ming Pao newspaper reported the release of the publication on high risk of liver cancer among immigrants with chronic hepatitis C.

March 12, 2012 Phone interview with Fairchild Radio (FM88.9) about the high risk of chronic hepatitis C among immigrants from developing countries.

This is Exhibit "D" referred to in the Affidavit of Murray Krahn sworn before me, this 16th day of March, 2015

A COMMISSIONER FOR TAKING AFFIDAVITS

CURRICULUM VITAE

Yi, Qi-long

Address:
30 Sturbridge PVT
Ottawa ON
K1T 3J7, Canada
Tel#: 613-680-6615 (Home)
613-739-2214 (Work)
E-mail: qi-long.yi@bloodservices.ca

EDUCATION:

9/1996 – 1999.	MSc. in Biostatistics, Public Health Sciences, University of Toronto, Canada
9/85 – 7/1990	Ph.D. in Medical Statistics. School of Public Health, Shanghai Medical University, China
9/1978 – 1/1982	Bachelor in Medicine, Yang Zhou Medical School, Yang Zhou University, China

WORK & RESEARCH EXPERIENCE:

8/2005 –	Senior Biostatistician, Canadian Blood Services; Adjunct professor, University of Toronto and University of Ottawa
1/2001 – 8/2005	Biostatistician. Princess Margaret Hospital
1/2001 – 8/2007	Associate professor. Public Health Sciences, University of Toronto
4/1999 – 1/2001	Biostatistician. Canadian Cardiovascular Collaboration. McMaster University
11/1997 – 1999	Statistical Consultant (part time), Pasteur Merieux Connaught Company (Aventis)
10/1992 – 3/1996	Research Fellow in Epidemiology. Purdue University, United States
6/1990 – 10/1992	Assistant Professor in Medical Statistics, School of Public Health, Shanghai Medical University, China

KNOWLEDGE AND PROFESSIONAL SKILLS:

- Statistics, Medicine (Internal Diseases) and Epidemiology
- Computer Skills: SAS and Splus, etc.

TEACHING EXPERIENCE:

- Taught **Statistics** at George Brown College in Toronto for one semester
- Teaching assistant in **Categorical Data Analysis** at University of Toronto, Canada
- Teaching assistant in **Biostatistics** at University of Toronto, Canada
- Teaching assistant in **Epidemiology** at Purdue University, US
- Taught **Medical Statistics** for two years at Shanghai Medical University
- Taught **Multivariate Analysis in Medical Statistics** for one year at Shanghai Medical University

AWARDS:

1997	Two years University of Toronto open scholarship
1992	Fogarty International Research Fellowship by the National Institutes of Health, U.S.A. (Post doctoral training in Epidemiology for two years)
1991	Ho,Yingdong National Young Teacher Prize ($1000) by HOYINGDONG Foundation in Hong Kong

REVIEWER:

1. American Journal of Epidemiology
2. Statistics in Medicine
3. Controlled Clinical Trials
4. Psychology
5. Vox Sanguinis
6. Grant review panel member for Office of the Chief Scientist, Innovative Science Competition, Health Canada in 2003-2004 and 2004-2005

PUBLICATIONS:

1. Yi Q, Wang PP, He Y. Reliability analysis for continuous measurements: Equivalence test for agreement. Stat Med. 2008 Jul 10;27(15):2816-25.
2. Yi Q. Panzarella T. Corey P. Incorporating the sampling variation of the disease prevalence when calculating the sample size in a study to determine the diagnostic accuracy of a test. . [Journal Article] *Controlled Clinical Trials. 2004* August 2004, Pages 417-427
3. Yi Q. Wang PP. Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. [Evaluation Studies. Journal Article] *Journal of Viral Hepatitis. 11(2):166-74, 2004 Mar.*
4. Yi Q. Panzarella T. Estimating sample size for tests on trends across repeated measurements with missing data based on the interaction term in a mixed model. [Journal Article] *Controlled Clinical Trials. 23(5):481-96, 2002 Oct.*
5. Yi Q. Zhang Z. The survival analyses of 2738 patients with simple pneumoconiosis. [Journal Article] *Occupational & Environmental Medicine. 53(2):129-35, 1996 Feb.*
6. Yi Q. Glickman LT. Computer simulation analysis of Sartwell's incubation period model for diseases with uncertain etiology. The effect of competing risk. [Journal Article] *American Journal of Epidemiology. 142(3):363-8, 1995 Aug* .
7. McKelvey K, Attonito J, Madhivanan P, Yi Q, Mzayek F, Maziak W. Nicotine Tob Res. Determinants of Cigarette Smoking Initiation in Jordanian Schoolchildren: Longitudinal Analysis. 2014 Aug 20
8. McKelvey K, Attonito J, Madhivanan P, Jaber R, Yi Q, Mzayek F, Maziak W. Determinants of waterpipe smoking initiation among school children in Irbid, Jordan: a 4-year longitudinal analysis. Drug Alcohol Depend. 2014 Sep 1;142:307-13
9. Taha M, Kalab M, Yi QL, Landry C, Greco-Stewart V, Brassinga AK, Sifri CD, Ramirez-Arcos S. Biofilm-forming skin microflora bacteria are resistant to the bactericidal action of disinfectants used during blood donation. Transfusion. 2014 Nov;54(11):2974-82
10. Alam A, Huang M, Yi QL, Lin Y, Hannach B. Perioperative transfusion-related acute lung injury: the Canadian Blood Services experience.
11. O'brien SF[1], Xi G[2], Fan W[2], Yi QL[1], Osmond L[2], Delage G[3], Goldman M[4] Are donors in Canada compliant with deferral for tattoos and piercing? Blood Transfus. 2014 Jan;12(1):141-2.
12. Hansen AL, Turner TR, Yi QL, Acker JP. Quality of red blood cells washed using an automated cell processor with and without irradiation. Transfusion. 2013 Nov 14.
13. Lieberman L, Maskens C, Cserti-Gazdewich C, Hansen M, Lin Y, Pendergrast J, Yi QL, Callum J. A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. Transfus Med Rev. 2013 Oct;27(4):206-12.
14. Mastronardi C, Schubert P, Levin E, Bhakta V, Yi QL, Hansen A, Stewart T, Jenkins C, Lefresne W, Sheffield W, Acker JP. Process improvement by eliminating mixing of whole blood units after an overnight hold prior to component production using the buffy coat method. J Blood Transfus. 2013;2013:154838.

15. O'Brien SF, Goldman M, Scalia V, Yi QL, Fan W, Xi G, Dines IR, Fearon MA. The epidemiology of human T-cell lymphotropic virus types I and II in Canadian blood donors. Transfus Med. 2013 Jul 17.
16. Lieberman L, Petraszko T, Yi QL, Hannach B, Skeate R. Transfusion-related lung injury in children: a case series and review of the literature. Transfusion. 2014 Jan;54(1):57-64.
17. O'Brien SF, Uzicanin S, Choquet K, Yi QL, Fan W, Goldman M. Impact of changes to policy for Mexican risk travel on Canadian blood donor deferrals. Blood Transfus. 2013 Oct;11(4):580-4.
18. O'Brien SF, Scalia V, Goldman M, Fan W, Yi QL, Huang M, Ndao M, Fearon MA. Evaluation of selective screening of donors for antibody to Trypanosoma cruzi: seroprevalence of donors who answer "no" to risk questions. Transfusion. 2014 Mar;54(3 Pt 2):863-9.
19. Hansen A, Yi QL, Acker JP. Quality of red blood cells washed using the ACP 215 cell processor: assessment of optimal pre- and postwash storage times and conditions. Transfusion. 2013 Mar 22. doi: 10.1111/trf.12170. [Epub ahead of print]
20. Chen Y, Mo F, Yi Q, Morrison H, Mao Y.Association between mental health and fall injury in Canadian immigrants and non-immigrants. Accid Anal Prev. 2013 Oct;59:221-6.
21. Cavalieri M, Schmidt R, Chen C, Mok V, de Freitas GR, Song S, Yi Q, Ropele S, Grazer A, Homayoon N, Enzinger C, Loh K, Wong KS, Wong A, Xiong Y, Chang HM, Wong MC, Fazekas F, Eikelboom JW, Hankey GJ; VITATOPS Trial Study Group. B vitamins and magnetic resonance imaging-detected ischemic brain lesions in patients with recent transient ischemic attack or stroke: the VITAmins TO Prevent Stroke (VITATOPS) MRI-substudy. Stroke. 2012 Dec;43(12):3266-70.
22. Gommans J[1], Yi Q, Eikelboom JW, Hankey GJ, Chen C, Rodgers H; VITATOPS trial study group. The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial. BMC Geriatr. 2013 Sep 3;13:88.
23. Chen Y, Mo F, Yi QL, Jiang Y, Mao Y. Unintentional injury mortality and external causes in Canada from 2001 to 2007. Chronic Dis Inj Can. 2013 Mar;33(2):95-102.
24. Ramirez-Arcos S, Perkins H, Kou Y, Mastronardi C, Kumaran D, Taha M, Yi QL, McLaughlin N, Kahwash E, Lin Y, Acker J. Bacterial growth in red blood cell units exposed to uncontrolled temperatures: challenging the 30-minute rule. Vox Sang. 2013 Feb 9. doi: 10.1111/vox.12027. [Epub ahead of print]
25. Goldman M, Osmond L, Yi QL, Cameron-Choi K, O'Brien SF. Frequency and risk factors for donor reactions in an anonymous blood donor survey. Transfusion. 2012 Dec 11. doi: 10.1111/trf.12011. [Epub ahead of print]
26. O'Brien SF, Shao ZJ, Osmond L, Yi QL, Li CY, An QX. Donor motivation in Xi'an, China: comparison with Canadian donors. Vox Sang. 2012 Oct 16.
27. O'Brien SF, Scalia V, Goldman M, Fan W, Yi QL, Dines IR, Huang M, Ndao M, Fearon MA Selective testing for Trypanosoma cruzi: the first year after implementation at Canadian Blood Services. Transfusion. 2012 Nov 12
28. Fan W, Yi QL, Xi G, Goldman M, Germain M, O'Brien SF.The impact of increasing the upper age limit of donation on the eligible blood donor population in Canada. Transfus Med. 2012 Dec;22(6):395-403.
29. Ramirez-Arcos S, Mastronardi C, Perkins H, Kou Y, Turner T, Mastronardi E, Hansen A, Yi QL, McLaughlin N, Kahwash E, Lin Y, Acker J. Evaluating the 4-hour and 30-minute rules: effects of room temperature exposure on red blood cell quality and bacterial growth. Transfusion. 2012 Jul 31.
30. Goldman M, Uzicanin S, Yi QL, Acker J, Ramirez-Arcos S. Validation and implementation of a new hemoglobinometer for donor screening at Canadian Blood Services. Transfusion. 2012 Jul;52(7 Pt 2):1607-13.
31. Acker JP, M Croteau I, Yi QL. An analysis of the bias in red blood cell hemolysis measurement using several analytical approaches. Clin Chim Acta. 2012 Nov 12;413(21-22):
32. Semple E, Bowes-Schmidt A, Yi QL, Shimla S, Devine DV. Transfusion reactions: a comparative observational study of blood components produced before and after implementation of semiautomated production from whole blood. Transfusion. 2012 Jun 28
33. O'Brien SF, Yi QL, Fan W, Scalia V, Fearon MA, Allain JP. Current incidence and residual risk of HIV, HBV and HCV at Canadian Blood Services. Vox Sang. 2012 Jul;103(1):83-6
34. Hankey GJ, Eikelboom JW, Yi Q, Lees KR, Chen C, Xavier D, Navarro JC, Ranawaka UK, Uddin W, Ricci S, Gommans J, Schmidt R; on behalf of the VITAmins TO Prevent Stroke (VITATOPS) Trial Study Group. Treatment With B Vitamins and Incidence of Cancer in Patients With Previous Stroke or Transient Ischemic Attack: Results of a Randomized Placebo-Controlled Trial. Stroke. 2012 Apr 3. [Epub ahead of print]
35. Goldman M, Yi QL, Ye X, Tessier L, O'Brien SF. Donor understanding and attitudes about current and potential deferral criteria for high-risk sexual behavior. 2011Transfusion. Page 1537-2995.
36. Greco CA, Zhang JG, Kalab M, Yi QL, Ramirez-Arcos SM, Gyongyossy-Issa MI. Effect of platelet additive solution on bacterial dynamics and their influence on platelet quality in stored platelet concentrates. Transfusion. 2010 Nov;50(11):2344-52.

37. VITATOPS Trial Study Group B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010 Sep;9(9):855-65. Epub 2010 Aug 3.
38. Palmer DS, O'Toole J, Montreuil T, Scalia V, Yi QL, Goldman M, Towns D. Screening of Canadian Blood Services donors for severe immunoglobulin A deficiency. Transfusion. 2010 Jul;50(7):1524-31. Epub 2010 Feb 11.
39. Cassinotti E, Melson J, Liggett T, Melnikov A, Yi Q, Replogle C, Mobarhan S, Boni L, Segato S, Levenson V. DNA methylation patterns in blood of patients with colorectal cancer and adenomatous colorectal polyps. Int J Cancer. 2011 Oct 23. doi: 10.1002/ijc.26484. [Epub ahead of print]
40. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. J Thromb Thrombolysis. 2011 Sep 15. [Epubahead of print]
41. Liggett TE, Melnikov A, Yi Q, Replogle C, Hu W, Rotmensch J, Kamat A, Sood AK, Levenson V. Distinctive DNA methylation patterns of cell-free plasma DNA in women with malignant ovarian tumors. Gynecol Oncol. 2011 Jan;120(1):113-20
42. Liggett T, Melnikov A, Yi QL, Replogle C, Brand R, Kaul K, Talamonti M, Abrams RA, Levenson V. Differential methylation of cell-free circulating DNA among patients with pancreatic cancer versus chronic pancreatitis. 2010 Apr 1;116(7):1674-80
43. Chen Y, Wu J, Yi QL. Reduced risk of hospitalization associated with influenza vaccination in Canada. Vaccine. 2010 Mar 8;28(11):2290-5
44. Liggett T, Melnikov A, Tilwalli S, Yi Q, Chen H, Replogle C, Feng X, Reder A, Stefoski D, Balabanov R, Levenson V. Methylation patterns of cell-free plasma DNA in relapsing-remitting multiple sclerosis. J Neurol Sci. 2010 Mar 15;290(1-2):16-21. Epub 2010 Jan 12
45. Mar Fan HG, Houédé-Tchen N, Chemerynsky I, Yi QL, Xu W, Harvey B, Tannock IF. Menopausal symptoms in women undergoing chemotherapy-induced and natural menopause: a prospective controlled study. 2010 May;21(5):983-7.
46. O'Brien SF, Xi G, Yi QL, Goldman M. Understanding non-disclosure of deferrable risk: a study of blood donors with a history of intravenous drug use. Transfus Med. 2010 Feb;20(1):15-21.
47. O'Brien SF, Fan W, Xi G, Yi QL, Goldman M. Evaluation of the confidential unit exclusion form: the Canadian Blood Services experience. Vox Sang. 2010 Feb;98(2):138-44.
48. Maurer-Spurej E, Labrie A, Pittendreigh C, Chipperfield K, Smith C, Heddle N, Liu Y, Yi QL, Barnett M. Platelet quality measured with dynamic light scattering correlates with transfusion outcome in hematologic malignancies.Transfusion. 2009 Nov;49(11):2276-84.
49. O'Brien SF, Yi QL, Fan W, Fearon MA, Scalia V, Goldman M. Impact of a policy to permit the return of donors repeat-reactive to the Abbott PRISM antibody to hepatitis B core antigen assay. Transfusion. 2009 Feb;49(2):271-7.
50. Goldman M, Xi G, Yi QL, Fan W, O'Brien SF. Reassessment of deferrals for tattooing and piercing. Transfusion. 2009 Feb;49(2):271-7.
51. Panton RL, Downie R, Truong T, Mackeen L, Kabene S, Yi QL, Chan HS, Gallie BL. A visual approach to providing prognostic information to parents of children with retinoblastoma. Psychooncology. 2009 Mar;18(3):300-4.
52. Thein HH, Yi Q, Heathcote EJ, Krahn MD. Prognosis of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort. J Viral Hepat. 2009 Apr 27.
53. Sumner G, Salehian O, Yi Q, Healey J, Mathew J, Al-Merri K, Al-Nemer K, Mann JF, Dagenais G, Lonn E. The Prognostic Significance of Bundle Branch Block in High-Risk Chronic Stable Vascular Disease Patients: A Report from the HOPE Trial. J Cardiovasc Electrophysiol. 2009 Feb 26..
54. Verhovsek M, Douketis JD, Yi Q, Shrivastava S, Tait RC, Baglin T, Poli D, Lim W. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Ann Intern Med. 2008 Oct 7;149(7):481-90, W94. Review.
55. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008 Oct 1;22(15):1979-91. Review.
56. VITATOPS Trial Study Group. VITATOPS, the VITAmins TO prevent stroke trial: rationale and design of a randomised trial of B-vitamin therapy in patients with recent transient ischaemic attack or stroke (NCT00097669) (ISRCTN74743444). Int J Stroke. 2007 May;2(2):144-50.
57. O'Brien SF, Xi G, Fan W, Yi QL, Fearon MA, Scalia V, Goldman M. Epidemiology of hepatitis B in Canadian blood donors . Transfusion. 2008 Nov;48(11):2323-30. Epub 2008 Jul 11.

58. Fan HG, Park A, Xu W, Yi QL, Braganza S, Chang J, Couture F, Tannock IF. The influence of erythropoietin on cognitive function in women following chemotherapy for breast cancer. Psychooncology. 2009 Feb;18(2):156-61.
59. Chen Y, Yi Q, Mao Y. Cluster of liver cancer and immigration: a geographic analysis of incidence data for Ontario 1998-2002. Int J Health Geogr. 2008 Jun 2;7:28.
60. Chen Y, Wu J, Yi Q, Huang G, Wong T. Depression associated with sexually transmitted infection (STI) in Canada . Sex Transm Infect. 2008 Dec;84(7):535-40.
61. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31. Review
62. O'Brien SF, Fan W, Xi G, Yi QL, Goldman M, Fearon MA, Infante-Rivard C, Chiavetta JA, Willems B, Pi D, Fast M, Delage G. Declining hepatitis C rates in first-time blood donors: insight from surveillance and case-control risk factor studies.Transfusion. 2008 May;48(5):902-9.
63. O'Brien SF, Ram SS, Yi QL, Goldman M. Donor's understanding of the definition of sex as applied to predonation screening questions.Vox Sang. 2008 May;94(4):329-33.
64. O'Brien SF, Chiavetta JA, Fan W, Xi G, Yi QL, Goldman M, Scalia V, Fearon MA. Assessment of a travel question to identify donors with risk of Trypanosoma cruzi: operational validity and field testing. Transfusion. 2008 Apr;48(4):755-61
65. Alegria JR, Miller TD, Gibbons RJ, Yi QL, Yusuf S; Collaborative Organization of RheothRx Evaluation (CORE) Trial Investigators. Infarct size, ejection fraction, and mortality in diabetic patients with acute myocardial infarction treated with thrombolytic therapy. Am Heart J. 2007 Oct;154(4):743-50.
66. O'brien SF, Fearon MA, Yi QL, Fan W, Scalia V, Muntz IR, Vamvakas EC.Hepatitis B virus DNA-positive, hepatitis B surface antigen-negative blood donations intercepted by anti-hepatitis B core antigen testing: the Canadian Blood Services experience. Transfusion. 2007 Oct;47(10):1809-15.
67. O'Brien SF, Yi QL, Fan W, Scalia V,Kleinman SH,Vamvakas EC. Current incidence and estimated residual risk of transfusion-transmitted infections in donations made to Canadian Blood Services.Transfusion. 2007 Feb;47(2):316-25.
68. Ray JG, Lonn E, Yi Q, Rathe A, Sheridan P, Kearon C; on behalf of the HOPE-2 investigators.Venous thromboembolism in association with features of the metabolic syndrome. QJM. 2007 Nov;100(11):679-84.
69. Chen Y, Yi QL, Wu J, Li F. Chronic disease status, self-perceived health and hospital admissions are important predictors for having a flu shot in Canada. Vaccine. 2007 Oct 16;25(42):7436-40.
70. Goldman M, Ram SS, Yi QL, Mazerall J, O'brien SF.The donor health assessment questionnaire: potential for format change and computer-assisted self-interviews to improve donor attention. Transfusion. 2007 Sep;47(9):1595-600.
71. Sadikov E, Bezjak A, Yi QL, Wells W, Dawson L, Millar BA, Laperriere N. Value of whole brain re-irradiation for brain metastases--single centre experience. Clin Oncol (R Coll Radiol). 2007 Sep;19(7):532-8.
72. Chung PW, Bristow RG, Milosevic MF, Yi QL, Jewett MA, Warde PR, Catton CN, McLean M, Moore M, Tannock IF, Gospodarowicz MK. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. Urol Oncol. 2007 Jul-Aug;25(4):303-9.
73. Uy KL, Darling G, Xu W, Yi QL, De Perrot M, Pierre AF, Waddell TK, Johnston MR, Bezjak A, Shepherd FA, Keshavjee S. Improved results of induction chemoradiation before surgical intervention for selected patients with stage IIIA-N2 non-small cell lung cancer. J Thorac Cardiovasc Surg. 2007 Jul;134(1):188-93.
74. Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E; Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial.
Ann Intern Med. 2007 Jun 5;146(11):761-7.
75. O'Brien SF, Yi QL, Fearon MA, Goldman M. A predonation screening question for occupational exposure to simian foamy virus: a preliminary donor survey in Canada. Transfusion. 2007 May;47(5):949-50.
76. Woods K, Douketis JD, Kathirgamanathan K, Yi Q, Crowther MA. Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. J Thromb Thrombolysis. 2007 Oct;24(2):93-7.
77. Sawka AM, Ray JG, Yi Q, Josse RG, Lonn E. Randomized clinical trial of homocysteine level lowering therapy and fractures.Arch Intern Med. 2007 Oct 22;167(19):2136-9. No abstract available
78. Lin RY,Pitt TJ, Lou WY, Yi Q Asthma hospitalization patterns in young children relating to admission age, infection presence, sex, and race. Ann Allergy Asthma Immunol. 2007 Feb;98(2):139-45.
79. Downie FP, Mar Fan HG, Houede-Tchen N, Yi Q, Tannock IF. Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: evaluation with patient interview after formal assessment. Psychooncology. 2006 Oct;15(10):921-30.

80. Goldman M, Ram SS, Yi QL ,O'Brien SF. The Canadian donor health assessment questionnaire: can it be improved?Transfusion. 2006 Dec;46(12):2169-75.
81. Zahariadis G, Plitt SS, O'brien S, Yi QL, Fan W, Preiksaitis JK. Prevalence and Estimated Incidence of Blood-Borne Viral Pathogen Infection in Organ and Tissue Donors from Northern Alberta. Am J Transplant. 2006 Nov 15;
82. Vardy J, Wong K, Yi QL, Park A,Maruff P, Wagner L, Tannock IF. Assessing cognitive function in cancer patients. Support Care Cancer. 2006 Nov;14(11):1111-8. Epub 2006 Mar 15.
83. Joly F, Alibhai SM, Galica J, Park A, Yi QL, Wagner L,Tannock IF. Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer. J Urol. 2006 Dec;176(6 Pt 1):2443-7.
84. Staton JM, Sayer MS, Hankey GJ, Attia J, Thakkinstian A, Yi Q, Cole VJ, Baker R, Eikelboom JW. Association between phosphodiesterase 4D gene and ischaemic stroke. J Neurol Neurosurg Psychiatry. 2006 Sep;77(9):1067-9.
85. Chang H, Yeung J, Brandwein J, Yi QL. CD7 expression predicts poor disease free survival and post-remission survival in patients with acute myeloid leukemia and normal karyotype. Leuk Res. 2006 Jul 10;
86. Gupta V, Brooker C, Tooze JA, Yi QL,Sage D, Turner D, Kangasabapathy P, Marsh JC. Clinical relevance of cytogenetic abnormalities at diagnosis of acquired aplastic anaemia in adults.
Br J Haematol. 2006 Jul;134(1):95-9.
87. Chang H, Yi QL. Acute myeloid leukemia with pseudo-Chediak-Higashi anomaly exhibits a specific immunophenotype with CD2 expression. Am J Clin Pathol. 2006 May;125(5):791-4.
88. Chen CI, Nanji S,Prabhu A, Beheshti R, Yi QL, Sutton D, Stewart AK. Sequential, cycling maintenance therapy for post transplant multiple myeloma. Bone Marrow Transplant. 2006 Jan;37(1):89-94.
89. Witkos M, Yi QL, Heathcote J, Kapral MK, Krahn MD. Predictors of antiviral therapy in a post-transfusion cohort of hepatitis C patients. Can J Gastroenterol. 2006 Feb;20(2):107-11
90. Chang H, Samiee S, Yi QL. Prognostic relevance of CD56 expression in multiple myeloma: a study including 107 cases treated with high-dose melphalan-based chemotherapy and autologous stem cell transplant. Leuk Lymphoma. 2006 Jan;47(1):43-7.
91. Fan HG, Houede-Tchen N, Yi QL, Chemerynsky I, Downie FP, Sabate K, Tannock IF. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. J Clin Oncol. 2005 Nov 1;23(31):8025-32.
92. Wang Y, Cummings B, Catton P, Dawson L, Kim J, Ringash J, Wong R, Yi QL, Brierley J. Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients.
Radiother Oncol. 2005 Nov;77(2):126-32. Epub 2005 Oct 10.
93. Gupta V, Daly A, Lipton JH, Hasegawa W, Chun K, Kamel-Reid S, Tsang R, Yi QL, Minden M, Messner H, Kiss T. Nonmyeloablative stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia in patients 60 years or older. Biol Blood Marrow Transplant. 2005 Oct;11(10):764-72.
94. Chang H, Qi XY, Samiee S, Yi QL, Chen C, Trudel S, Mikhael J, Reece D, Stewart AK. Genetic risk identifies multiple myeloma patients who do not benefit from autologous stem cell transplantation. Bone Marrow Transplant. 2005 Nov;36(9):793-6.
95. Carolan H, Sun AY, Bezjak A, Yi QL, Payne D, Kane G, Waldron J, Leighl N, Feld R, Burkes R, Keshavjee S, Shepherd F. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? Lung Cancer. 2005 Jul;49(1):109-15. Epub 2005 Feb 2.
96. Brandwein JM, Gupta V, Wells RA, Schuh AC, Schimmer AD, Lipton JH, Messner HA, Yi QL, Chun K, Kamel-Reid S, Minden MD. Treatment of elderly patients with acute lymphoblastic leukemia--evidence for a benefit of imatinib in BCR-ABL positive patients. Leuk Res. 2005 Dec;29(12):1381-6. Epub 2005 May 31.
97. Chang H, Samiee S, Yi QL.Prognostic relevance of CD56 expression in multiple myeloma: A study including 107 cases treated with high-dose melphalan-based chemotherapy and autologous stem cell transplant. Leuk Lymphoma. 2006 Jan;47(1):43-7.
98. Chang H, Bartlett ES, Patterson B, Chen CI, Yi QL. The absence of CD56 on malignant plasma cells in the cerebrospinal fluid is the hallmark of multiple myeloma involving central nervous system. Br J Haematol. 2005 May;129(4):539-41.
99. Gupta V, Chun K, Yi QL, Minden M, Schuh A, Wells R, Brandwein J. Disease biology rather than age is the most important determinant of survival of patients > or = 60 years with acute myeloid leukemia treated with uniform intensive therapy. Cancer. 2005 May 15;103(10):2082-90.
*100.*Gupta V, Gordon-Smith EC, Cook G, Parker A, Duguid JK, Wilson KM, Yi QL, Marsh JC. A third course of anti-thymocyte globulin in aplastic anaemia is only beneficial in previous responders. Br J Haematol. 2005 Apr;129(1):110-7.

101. Mann JF, Yi QL, Sleight P, Dagenais GR, Gerstein HC, Lonn EM, Bosch J; HOPE Investigators. Serum potassium, cardiovascular risk, and effects of an ACE inhibitor: results of the HOPE study. Clin Nephrol. 2005 Mar;63(3):181-7.
102. Eikelboom JW, Hankey GJ, Thom J, Claxton A, Yi Q, Gilmore G, Staton J, Barden A, Norman PE. Enhanced antiplatelet effect of clopidogrel in patients whose platelets are least inhibited by aspirin: a randomized crossover trial.J Thromb Haemost. 2005 Dec;3(12):2649-55.
103. Darling GE, Abdurahman A, Yi QL, Johnston M, Waddell TK, Pierre A, Keshavjee S, Ginsberg R. Risk of a right pneumonectomy: role of bronchopleural fistula. Ann Thorac Surg. 2005 Feb;79(2):433-7.
104. Krahn MD, John-Baptiste A, Yi Q, Doria A, Remis RS, Ritvo P, Friedman S. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. Vaccine. 2005 Feb 18;23(13):1549-58.
105. Chang H, Stewart AK, Qi XY, Li ZH, Yi QL, Trudel S. Immunohistochemistry accurately predicts FGFR3 aberrant expression and t(4;14) in multiple myeloma.Blood. 2005 Mar 10; [Epub ahead of print]
106. Dagenais GR, Yi Q, Lonn E, Sleight P, Ostergren J, Yusuf S; on behalf of the HOPE Trial Investigators. Impact of cigarette smoking in high-risk patients participating in a clinical trial. A substudy from the Heart Outcomes Prevention Evaluation (HOPE) trial. Eur J Cardiovasc Prev Rehabil. 2005 Feb;12(1):75-81.
107. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J. 2005 Jan;149(1):54-60.
108. Hankey GJ, Eikelboom JW, Loh K, Tang M, Pizzi J, Thom J, Yi Q. Sustained homocysteine-lowering effect over time of folic acid-based multivitamin therapy in stroke patients despite increasing folate status in the population. Cerebrovasc Dis. 2005;19(2):110-6. Epub 2004 Dec 17.
109. Gupta V, Ball SE, Yi QL, Sage D, McCann SR, Lawler M, Ortin M, Freires M, Hale G, Waldmann H, Gordon-Smith EC, Marsh JC. Favorable effect on acute and chronic graft-versus-host disease with cyclophosphamide and in vivo anti-CD52 monoclonal antibodies for marrow transplantation from HLA-identical sibling donors for acquired aplastic anemia. Biol Blood Marrow Transplant. 2004 Dec;10(12):867-76.
110. Dusitanond P, Eikelboom JW, Hankey GJ, Thom J, Gilmore G, Loh K, Yi Q, Klijn CJ, Langton P, van Bockxmeer FM, Baker R, Jamrozik K. Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: a randomized substudy of the VITATOPS trial. Stroke. 2005 Jan;36(1):144-6. Epub 2004 Nov 29.
111. Thom J, Gilmore G, Yi Q, Hankey GJ, Eikelboom JW. Measurement of soluble P-selectin and soluble CD40 ligand in serum and plasma. J Thromb Haemost. 2004 Nov;2(11):2067-9. No abstract available.
112. Gupta V, Yi QL, Brandwein J, Lipton JH, Messner HA, Schuh AC, Wells RA, Minden MD. Role of all-trans-retinoic acid (ATRA) in the consolidation therapy of acute promyelocytic leukaemia (APL).
Leuk Res. 2005 Jan;29(1):113-4.
113. Mann JF, Yi QL, Gerstein HC. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. Kidney Int Suppl. 2004 Nov;(92):S59-62. Review.
114. Chang H, Qi C, Yi QL, Reece D, Stewart AK. p53 gene deletion detected by fluorescence in situ hybridization is an adverse prognostic factor for patients with multiple myeloma following autologous stem cell transplantation. Blood. 2005 Jan 1;105(1):358-60. Epub 2004 Aug 31.
115. Hankey GJ, Eikelboom JW, Loh K, Yi Q, Pizzi J, Tang M, Hickling S, Le M, Klijn CJ, Dusitanond P, van Bockxmeer F, Gelavis A, Baker R, Jamrozik K. Is there really a power shortage in clinical trials testing the "homocysteine hypothesis?". Arterioscler Thromb Vasc Biol. 2004 Aug;24(8):e147. No abstract available.
116. Chang H, Brandwein J, Yi QL, Chun K, Patterson B, Brien B. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. Leuk Res. 2004 Oct;28(10):1007-11.
117. Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, Lonn E, Teo K, McQueen M, Yusuf S. C-reactive protein as a screening test for cardiovascular risk in a multiethnic population.
Arterioscler Thromb Vasc Biol. 2004 Aug;24(8):1509-15. Epub 2004 Jun 17.
118. Lonn E. Shaikholeslami R. Yi Q. Bosch J. Sullivan B. Tanser P. Magi A. Yusuf S. Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the Heart Outcomes Prevention Evaluation (HOPE) Trial.[see comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Journal of the American College of Cardiology. 43(12):2200-6, 2004 Jun 16.*
119. Theal M. Sleik K. Anand S. Yi Q. Yusuf S. Lonn E. Prevalence of mitral valve prolapse in ethnic groups. [Journal Article] *Canadian Journal of Cardiology. 20(5):511-5, 2004 Apr.*
120. Gupta V. Yi QL. Brandwein J. Minden MD. Schuh AC. Wells RA. Chun K. Kamel-Reid S. Tsang R. Daly A. Kiss T. Lipton JH. Messner HA. The role of allogeneic bone marrow transplantation in adult patients below the age

of 55 years with acute lymphoblastic leukemia in first complete remission: a donor vs no donor comparison. [Journal Article] *Bone Marrow Transplantation. 33(4):397-404, 2004 Feb.*
121. Theal M. Sleik K. Anand S. Yi Q. Yusuf S. Lonn E. Prevalence of mitral valve prolapse in ethnic groups. [Journal Article] *Canadian Journal of Cardiology. 20(5):511-5, 2004 Apr.*
122. Chang H. Sloan S. Li D. Zhuang L. Yi QL. Chen CI. Reece D. Chun K. Keith Stewart A. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. [Journal Article] *British Journal of Haematology. 125(1):64-8, 2004 Apr.*
123. Mann JF. Gerstein HC. Yi QL. Franke J. Lonn EM. Hoogwerf BJ. Rashkow A. Yusuf S. HOPE Investigators. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *American Journal of Kidney Diseases. 42(5):936-42, 2003 Nov.*
124. Chang H. Salma F. Yi QL. Patterson B. Brien B. Minden MD. Prognostic relevance of immunophenotyping in 379 patients with acute myeloid leukemia. [Journal Article] *Leukemia Research. 28(1):43-8, 2004 Jan.*
125. Cole VJ. Staton JM. Eikelboom JW. Hankey GJ. Yi Q. Shen Y. Berndt MC. Baker RI. Collagen platelet receptor polymorphisms integrin alpha2beta1 C807T and GPVI Q317L and risk of ischemic stroke. [Journal Article] *Journal of Thrombosis & Haemostasis. 1(5):963-70, 2003 May.*
126. Dagenais GR. Auger P. Bogaty P. Gerstein H. Lonn E. Yi Q. Yusuf S. HOPE Study Investigators. Increased occurrence of diabetes in people with ischemic cardiovascular disease and general and abdominal obesity. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Canadian Journal of Cardiology. 19(12):1387-91, 2003 Nov.*
127. Tchen N. Juffs HG. Downie FP. Yi QL. Hu H. Chemerynsky I. Clemons M. Crump M. Goss PE. Warr D. Tweedale ME. Tannock IF. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. [Journal Article] *Journal of Clinical Oncology. 21(22):4175-83, 2003 Nov 15.*
128. McQuillan AM. Eikelboom JW. Hankey GJ. Baker R. Thom J. Staton J. Yi Q. Cole V. Protein Z in ischemic stroke and its etiologic subtypes. [Journal Article] *Stroke. 34(10):2415-9, 2003 Oct.*
129. Kelemen LE. Anand SS. Vuksan V. Yi Q. Teo KK. Devanesen S. Yusuf S. SHARE Investigators. Development and evaluation of cultural food frequency questionnaires for South Asians, Chinese, and Europeans in North America. [Evaluation Studies. Journal Article] *Journal of the American Dietetic Association. 103(9):1178-84, 2003 Sep.*
130. Cherian P. Hankey GJ. Eikelboom JW. Thom J. Baker RI. McQuillan A. Staton J. Yi Q. Endothelial and platelet activation in acute ischemic stroke and its etiological subtypes. [Journal Article] *Stroke. 34(9):2132-7, 2003 Sep.*
131. Tchen N. Bedard P. Yi QL. Klein M. Cella D. Eremenco S. Tannock IF. Quality of life and understanding of disease status among cancer patients of different ethnic origin. [Journal Article] *British Journal of Cancer. 89(4):641-7, 2003 Aug 18.*
132. Chen X. Oza AM. Kusenda Z. Yi QL. Kochman D. Moore MJ. Davis AJ. Siu LL. Phase I study of cisplatin, irinotecan, and epirubicin administered every 3 weeks in patients with advanced solid tumours. [Clinical Trial. Clinical Trial, Phase I. Journal Article] *British Journal of Cancer. 89(4):617-24, 2003 Aug 18.*
133. Anand SS. Yi Q. Gerstein H. Lonn E. Jacobs R. Vuksan V. Teo K. Davis B. Montague P. Yusuf S. Study of Health Assessment and Risk in Ethnic Groups. Study of Health Assessment and Risk Evaluation in Aboriginal Peoples Investigators. Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. [Journal Article] *Circulation. 108(4):420-5, 2003 Jul 29.*
134. Gupta V. Minden MD. Yi QL. Brandwein J. Chun K. Prognostic significance of trisomy 4 as the sole cytogenetic abnormality in acute myeloid leukemia. [Review] [58 refs] [Case Reports. Journal Article. Review. Review of Reported Cases] *Leukemia Research. 27(11):983-91, 2003 Nov.*
135. Wang P. Yi Q. Scully L. Heathcote J. Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. [Journal Article] *Canadian Journal of Gastroenterology. 17(3):183-6, 2003 Mar.*
136. Hasegawa W. Lipton JH. Messner HA. Jamal H. Yi QL. Daly AS. Kotchetkova N. Kiss TL. Influence of one human leukocyte antigen mismatch on outcome of allogeneic bone marrow transplantation from related donors. [Review] [21 refs] [Journal Article. Review. Review, Multicase] *Hematology. 8(1):27-33, 2003 Feb.*
137. Mann JF. Gerstein HC. Yi QL. Lonn EM. Hoogwerf BJ. Rashkow A. Yusuf S. Development of renal disease in people at high cardiovascular risk: results of the HOPE randomized study. [Clinical Trial. Journal Article. Randomized Controlled Trial] *Journal of the American Society of Nephrology. 14(3):641-7, 2003 Mar.*
138. Anand SS. Razak F. Vuksan V. Gerstein HC. Malmberg K. Yi Q. Teo KK. Yusuf S. Diagnostic strategies to detect glucose intolerance in a multiethnic population. [Evaluation Studies. Journal Article] *Diabetes Care. 26(2):290-6, 2003 Feb.*

139. Eikelboom JW, Hankey GJ, Baker RI, McQuillan A, Thom J, Staton J, Cole V, Yi Q. C-reactive protein in ischemic stroke and its etiologic subtypes.J Stroke Cerebrovasc Dis. 2003 Mar-Apr;12(2):74-81.
140. Smieja M. Gnarpe J. Lonn E. Gnarpe H. Olsson G. Yi Q. Dzavik V. McQueen M. Yusuf S. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Multiple infections and subsequent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study.[see comment]. [Journal Article] *Circulation. 107(2):251-7, 2003 Jan 21.*
141. Rayan G. Dawson LA. Bezjak A. Lau A. Fyles AW. Yi QL. Merante P. Vallis KA. Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy.[see comment]. [Clinical Trial. Journal Article. Randomized Controlled Trial] *International Journal of Radiation Oncology, Biology, Physics. 55(1):154-61, 2003 Jan 1.*
142. Gerstein HC. Anand S. Yi QL. Vuksan V. Lonn E. Teo K. Malmberg K. McQueen M. Yusuf S. SHARE Investigators. The relationship between dysglycemia and atherosclerosis in South Asian, Chinese, and European individuals in Canada: a randomly sampled cross-sectional study. [Journal Article] *Diabetes Care. 26(1):144-9, 2003 Jan.*
143. Veres A. Fust G. Smieja M. McQueen M. Horvath A. Yi Q. Biro A. Pogue J. Romics L. Karadi I. Singh M. Gnarpe J. Prohaszka Z. Yusuf S. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Relationship of anti-60 kDa heat shock protein and anti-cholesterol antibodies to cardiovascular events.[see comment]. [Journal Article] *Circulation. 106(22):2775-80, 2002 Nov 26.*
144. Lonn E. Yusuf S. Hoogwerf B. Pogue J. Yi Q. Zinman B. Bosch J. Dagenais G. Mann JF. Gerstein HC. HOPE Study. MICRO-HOPE Study. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Diabetes Care. 25(11):1919-27, 2002 Nov.*
145. Lonn E. Roccaforte R. Yi Q. Dagenais G. Sleight P. Bosch J. Suhan P. Micks M. Probstfield J. Bernstein V. Yusuf S. HOPE Investigators. Heart Outcomes Prevention Evaluation. Effect of long-term therapy with ramipril in high-risk women. [Clinical Trial. Evaluation Studies. Journal Article. Randomized Controlled Trial] *Journal of the American College of Cardiology. 40(4):693-702, 2002 Aug 21.*
146. Gupta M. Doobay AV. Singh N. Anand SS. Raja F. Mawji F. Kho J. Karavetian A. Yi Q. Yusuf S. Risk factors, hospital management and outcomes after acute myocardial infarction in South Asian Canadians and matched control subjects.[see comment]. [Journal Article] *CMAJ Canadian Medical Association Journal. 166(6):717-22, 2002 Mar 19.*
147. Eikelboom JW. Hirsh J. Weitz JI. Johnston M. Yi Q. Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events.[see comment]. [Journal Article] *Circulation. 105(14):1650-5, 2002 Apr 9.*
148. Anand SS. Yusuf S. Jacobs R. Davis AD. Yi Q. Gerstein H. Montague PA. Lonn E. Risk factors, atherosclerosis, and cardiovascular disease among Aboriginal people in Canada: the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP).[see comment]. [Journal Article] *Lancet. 358(9288):1147-53, 2001 Oct 6.*
149. Mathew J. Sleight P. Lonn E. Johnstone D. Pogue J. Yi Q. Bosch J. Sussex B. Probstfield J. Yusuf S. Heart Outcomes Prevention Evaluation (HOPE) Investigators. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril.[see comment]. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Circulation. 104(14):1615-21, 2001 Oct 2.*
150. Dagenais GR. Yusuf S. Bourassa MG. Yi Q. Bosch J. Lonn EM. Kouz S. Grover J. HOPE Investigators. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Circulation. 104(5):522-6, 2001 Jul 31.*
151. Gerstein HC. Mann JF. Yi Q. Zinman B. Dinneen SF. Hoogwerf B. Halle JP. Young J. Rashkow A. Joyce C. Nawaz S. Yusuf S. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals.[see comment]. [Journal Article. Multicenter Study] *JAMA. 286(4):421-6, 2001 Jul 25.*
152. Ho SC. Chan SG. Yi Q. Wong E. Leung PC. Soy intake and the maintenance of peak bone mass in Hong Kong Chinese women. [Clinical Trial. Journal Article] *Journal of Bone & Mineral Research. 16(7):1363-9, 2001 Jul.*
153. Lonn E. Yusuf S. Dzavik V. Doris C. Yi Q. Smith S. Moore-Cox A. Bosch J. Riley W. Teo K. SECURE Investigators. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). [Clinical Trial. Journal Article. Randomized Controlled Trial] *Circulation. 103(7):919-25, 2001 Feb 20.*

154. Whaley DA. Attfield MD. Bedillion EJ. Walter KM. Yi Q. Regression method to estimate provisional TLV/WEEL-equivalents for non-carcinogens. [Journal Article] *Annals of Occupational Hygiene. 44(5):361-74, 2000 Aug.*
155. Ho SC. Chan SG. Yip YB. Cheng A. Yi Q. Chan C. Menopausal symptoms and symptom clustering in Chinese women. [Journal Article] *Maturitas. 33(3):219-27, 1999 Dec 15.*
156. Schellenberg D. Yi Q. Glickman NW. Glickman LT. Influence of thoracic conformation and genetics on the risk of gastric dilatation-volvulus in Irish setters. [Journal Article] *Journal of the American Animal Hospital Association. 34(1):64-73, 1998 Jan-Feb.*
157. Miller TD. Piegas LS. Gibbons RJ. Yi C. Yusuf S. Role of infarct size in explaining the higher mortality in older patients with acute myocardial infarction. [Journal Article] *American Journal of Cardiology. 90(12):1370-4, 2002 Dec 15.*
158. Mehta SR. Eikelboom JW. Rupprecht HJ. Lewis BS. Natarajan MK. Yi C. Pogue J. Yusuf S. Efficacy of hirudin in reducing cardiovascular events in patients with acute coronary syndrome undergoing early percutaneous coronary intervention.[see comment]. [Clinical Trial. Journal Article. Randomized Controlled Trial] *European Heart Journal. 23(2):117-23, 2002 Jan.*
159. Eikelboom JW. Anand SS. Mehta SR. Weitz JI. Yi C. Yusuf S. Prognostic significance of thrombocytopenia during hirudin and heparin therapy in acute coronary syndrome without ST elevation: Organization to Assess Strategies for Ischemic Syndromes (OASIS-2)study. [Clinical Trial. Journal Article. Randomized Controlled Trial] *Circulation. 103(5):643-50, 2001 Feb 6.*
160. Mehta SR. Eikelboom JW. Natarajan MK. Diaz R. Yi C. Gibbons RJ. Yusuf S. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. [Clinical Trial. Journal Article. Meta-Analysis. Multicenter Study. Randomized Controlled Trial] *Journal of the American College of Cardiology. 37(1):37-43, 2001 Jan.*
161. Anand SS. Yusuf S. Vuksan V. Devanesen S. Teo KK. Montague PA. Kelemen L. Yi C. Lonn E. Gerstein H. Hegele RA. Differences in risk factors, atherosclerosis and cardiovascular disease between ethnic groups in Canada: the study of health assessment and risk in ethnic groups (SHARE). [Journal Article] *Indian Heart Journal. 52(7 Suppl):S35-43, 2000 Nov-Dec.*
162. Anand SS. Yusuf S. Vuksan V. Devanesen S. Teo KK. Montague PA. Kelemen L. Yi C. Lonn E. Gerstein H. Hegele RA. McQueen M. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE)[see comment]. [Journal Article] *Lancet. 356(9226):279-84, 2000 Jul 22.*

PUBLICATIONS in Chinese:

163. Yi,Qi-long, Zhang Zhao-huan: A Multistate model for prognostic Analysis of Patients with Pneumoconiosis. ACTA Med.Shanghai, 1991.7
164. Yi,Qi-long, Zhang Zhao-huan: A three state model for analyzing the relationship between cumulative exposure to dust and response. Chinese J Prev. Med., 1992,26(5):278-80
165. Yi,Qi-long, Quian Wendy, Zhang Zhao-huan: Chiang's model for Survival data and it's application in the relation of dose- response. Applied Probability Statistics, 1991.3
166. Yi,Qi-long: Dynamics of inhaled dust particle in lung, ACTA Med. Shanghai, 1989.2
167. Yi,Qi-long, Zhang Zhao-huan: Method for evaluation of life length of silicotic patients , J. Lab. Med. 1989.4
168. Yi,Qi-long, Zhang Zhao -huan , Analysis of the prognosis of coal miners' pneumoconiosis with multistate model. J.Lab. Med. 1991
169. Yi,Qi-long, Estimation of the tumor incidence and prevalence based on the registered death information using multistate model. ACTA Med. Shanghai (suppl.). 1992.12.: 157-`58
170. Yi,Qi-long et al, Life Quality of elder people (>=65) in Shanghai County, Chinese J. Aged Med. 1993, 13(2):108-109
171. Lu Zhi-yin, Yi,Qi-long, Epidemiological investigation of prevalence of silicosis in Shanghai First Refractory Plant. Chinese J. Prev. Med., 1991
172. Wang Zhe-yao, Yi, Qi-long, ... The impact of age on prognoses in cirrhosis patients. Chinese J. Int. 1991
173. Fan Zhen,..,Yi, Qi-long,.., Factors influencing the effect of Radio- immunotherapy on liver cancer. ACTA Med. Shanghai, 1990.11 Vol.17
174. Wang Zhe-yao,...,Yi,Qi-long, An analysis of prognostic factors in cirrhosis. Chinese J. Dig. 1989.7

BOOK or JOURNAL PUBLICATIONS in Chinese:

1. **Yi, Qilong**, Multilevel analysis, in <<Applied Methods for Medical Research>> by Wang JH. Published in Peiking China , 2003, P464-480.

2. **Yi,Qi-long,** Survival analysis, In Encyclopedia of Medicine in China, Vol. I, Preventive Medicine. Edited by Gu Xueqi et al. Published by Shanghai Scientific and Technological Publish Co. 1992, P355-361.

3. Cai Wen-Wei, Yu Shun-Zhang and **Yi, Qilong** (Editors). ACTA ACADEMIAE MEDICINAE SHANGHAI, Vol.20, Supplement (Health Service in Shanghai Country) 1993.

4. Shong Weiming, Cao Shuhua and **Yi, Qilong**. <<Multivariate Analysis in Medical Statistics>>, Published by Shanghai Medical University Press. 1993

This is Exhibit "E" referred to in the
Affidavit of Murray Krahn
sworn before me,
this 16th day of March, 2015

A COMMISSIONER FOR TAKING AFFIDAVITS

CURRICULUM VITAE
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Personal Information

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Education

- 2009 – 2012, Postdoctoral Fellow in Medical Decision Making and Health Economics, Institute of Health Policy, Management & Evaluation, University of Toronto, Toronto, Ontario, Canada
- 2002 – 2009, Ph.D. in Computer Science (Pharmacoinformatics), University of Waterloo, Ontario, Canada
- 1999 – 2000, M.Math. in Computer Science (Database), University of Waterloo, Ontario, Canada
- 1995 – 1999, B.Sc. in Computer Science and Statistics, York University, Ontario, Canada

Academic Appointment

- 2013 – current, Assistant Professor (status), Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
- 2012 – current, Research Scientist, Toronto Health Economics and Technology Assessment Collaborative, University of Toronto, Ontario, Canada

External Grant

- **Wong W.W.L.** (PI), Krahn M., Bruneau J., Feld J., Feng Z.Z., Lee S.S., Mitsakakis, N. Myers, R.P., Pechlivanoglous, P., Powis, J., Rac, V.E. Cross sectional and longitudinal measures of quality of life and utility among patients with chronic hepatitis C virus infection, *Canadian Institutes of Health Research (CIHR) Operating Grant*, Ottawa, Ontario, Canada. ($100,000) 2014 – 2015.
- **Wong W.W.L.** (PI), Sander B., Deeks S., Murphy K.J. Canadian Partnership Against Cancer's (CPAC) Cancer Risk Management Model (CRMM) Evaluation Case Study: The Cost-Effectiveness of Integrated Cervical Cancer Prevention Strategies in Ontario, Canadian Partnership Again Cancer, Toronto, Ontario, Canada ($15,000) 2014.
- Chan K., Feld J., Hicks L., Krahn M., Pritchard K., **Wong W.W.L.** Clinical Effectiveness and Cost-Effectiveness of HBV Screening Before Adjuvant Chemotherapy in Patients with Early Stage Breast Cancer: A Modeling Perspective, *Canadian Breast Cancer Foundation Research Project Grant*, Toronto, Ontario, Canada. ($105,040) 2013– 2014.

- Thein H., Dore G., Earle C.C., Feld J., Fisman D.N., Krahn M., **Wong W.W.L.** A pharmacoeconomic policy model for hepatitis C: development and applications, *Canadian Institutes of Health Research (CIHR) Operating Grant*, Ottawa, Ontario, Canada. ($133,475) 2011 – 2013.
- Thein H., Earle C.C., Isaranuwatchai W., Oliverira C., Tinmouth J., **Wong W.W.L.** Canadian Partnership Against Cancer's (CPAC) Cancer Risk Management Model (CRMM) Evaluation Case Study: Prevention for Colorectal Cancer, Canadian Partnership Again Cancer, Toronto, Ontario, Canada ($15,000) 2011.

External Grant Under Review

- **Wong W.W.L.** (PI). Computational Methods in Drug Discovery, *Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant*, Ottawa, Ontario, Canada. ($210,750) 2015 – 2020.
- **Wong W.W.L.** (PI). Better Health System through Computation, *Canadian Institutes of Health Research (CIHR) New Investigator Award,* Ottawa, Ontario, Canada. ($300,000) 2015 – 2020.
- Rac V., Abrahamyan L., Carcone S., Fan I., Krahn M., Shahid N. Sahakyan Y. **Wong W.W.L.** Evaluation of Telehomecare Intervention for Patients with Heart Failure. Heart and Stroke Foundation of Canada (HSFC) Grants-in-Aid ($295,011) 2015 – 2018.
- Rac V., Abrahamyan L., Fan I., Krahn M., Shahid N. Sahakyan Y. **Wong W.W.L.** Evaluation of Telehomecare for patients with Heart Failure or Chronic Obstructive Pulmonary Disease. *Technology evaluation in the elderly network (TVN) Catalyst Grant Program.* ($100,000) 2015 – 2016.

Publications and Presentations

Refereed Journal

- **Wong W.W.L.**, Tu H-A., Feld, J., Wong, T., Krahn M. (2015). Cost-Effectiveness of Screening Hepatitis C in Canada. *Canadian Medical Association Journal (CMAJ)*, v187, 3:E110.
- Lee E.K, **Wong W.W.L.**, Trudeau M.E., Chan K.K. (2015). Cost-Effectiveness of Prophylactic Granulocyte Colony-Stimulating Factor for Febrile Neutropenia in Breast Cancer Patients Receiving FEC-D. *Breast Cancer Research and Treatment*, in press.
- Sander B., Ormanidhi O., **Wong W.W.L.**, Atkin, K., Murphy, J., Krahn M., and Deeks S. L. (2015). The Cost-Effectiveness of Integrated Cervical Cancer Prevention Strategies in the Ontario Setting – Can We Do Better? *International Journal of Cancer*, Revision Requested.
- **Wong W.W.L.**, Hicks L.K., Tu H-A, Pritchard K.I., Krahn M.D., Feld, J., Chan K.K.. (2015). Hepatitis B Virus Screening before Adjuvant Chemotherapy in Patients with Early Stage Breast Cancer: A Cost-Effectiveness Analysis. *Journal of the National Cancer Institute*, submitted.
- Riesco-Martinez M.C., Berry S., Ko Y., Mittmann N., Giotis A., Lien K., **Wong W.W.L.**, and Chan K.K. (2015). Cost effectiveness analysis of the use of EGFR

inhibitors for wild type (WT) KRAS unresectable metastatic Colorectal Cancer (mCRC). *Journal of Clinical Oncology*, submitted.

- Wijeysundera H., **Wong W.W.L.**, Bennell M., Fremes S. E., Radhakrishnan S., Peterson M., Ko, D.T. (2014). Impact of increasing wait times on the effectiveness of transcatheter aortic-valve replacement (TAVR) in high-risk and inoperable patients with severe aortic disease: a discrete event simulation model. *The Canadian Journal of Cardiology*, v30 10:1162-1169.
- **Wong W.W.L.**, Griesman, J., Feng, Z. (2014). Imputing Genotypes Using Regularized Generalized Linear Regression Models. *Statistical Applications in Genetics and Molecular Biology*, v13 5:519-529.
- **Wong W.W.L.**, Woo, G., Heathcote J.E., Krahn M. (2013). Disease Burden of Chronic Hepatitis B among Immigrants in Canada. *Canadian Journal of Gastroenterology*, v27, 3:137-147.
- Oliverira C., Nguyen V.H., Wijeysundera H., **Wong W.W.L.**, Woo, G., Grootendorst P., Liu P., Krahn M. (2013). Estimating the payoffs from cardiovascular disease research in Canada: an economic analysis. *CMAJ Open*, v1, 2:E83:E90.
- Nguyen V.H., Oliverira C., Wijeysundera H., **Wong W.W.L.**, Woo, G., Grootendorst P., Liu P., Krahn M. (2013). Canada's Contribution to Global Research in Cardiovascular Diseases. *The Canadian Journal of Cardiology*, v29, 6:742-746.
- Oliverira C., Nguyen V.H., Wijeysundera H., **Wong W.W.L.**, Woo, G., Liu P., Krahn M. (2012). How Much Are We Really Spending? The Estimation of the Expenditures on Cardiovascular Disease Research in Canada. *BMC Health Services Research*, v12:281.
- **Wong W.W.L.** and Burkowski F. J. (2011). Using Kernel Alignment to Select Features of Molecular Descriptors in a QSAR study, *IEEE Transactions on Computational Biology and Bioinformatics*, v8, 5:1373–1384.
- Feng Z., **Wong W.W.L.**, Gao X., Schenkel F. (2011). Generalized Genetic Association Study with Samples of related subjects, *Annals of applied statistics*, v5, 3:2109–2130.
- **Wong W.W.L.**, Woo, G., Heathcote J.E., Krahn M. (2011). Cost Effectiveness of Screening Immigrants to Canada for Hepatitis B. *Liver International*, v31, 8:1179–1190.
- **Wong W.W.L.** and Burkowski F. J. (2009). Predicting Multiple Binding Modes Using a Kernel Method Based on a Vector Space Model Molecular Descriptor, *International Journal of Computational Biology and Drug Design*, v2, 1:58–80.
- **Wong W.W.L.** and Burkowski F. J. (2009). A Constructive Approach for Discovering New Drug Leads: Using a Kernel Methodology for the Inverse-QSAR Problem, *Journal of ChemInformatics*, v1:4

Reports

- **Wong W.W.L**, Khoo E., Deeks S.L., Murphy J. and Sander B.. (2014). The Cost-Effectiveness of Integrated Cervical Cancer Prevention Strategies in Ontario. Canadian Partnership Against Cancer

- Murphy G., Farah B., **Wong W.W.L.**, Krahn M., Wells G., Chen L., Kelly S., Kaunėlis D., Blouin J., Carrie A.. (2014). CADTH THERAPEUTIC REVIEW: Scientific Report: Direct Acting Antiviral Agents for Chronic Hepatitis C Genotype 1. Canadian Agency for Drugs and Technologies in Health
- **Wong W.W.L.**, Tu H.A., Chen W., Feld J., Krahn M... (2013). Cost-Effectiveness of Screening Hepatitis C in Canada. Toronto Health Economics and Technology Assessment Collaborative
- **Wong W.W.L.**, Tu H.A., Chen W., Feld J., Krahn M.. (2013). Development of an Economic Policy Model for Hepatitis C. Toronto Health Economics and Technology Assessment Collaborative

Dissertation

- **Wong W. W. L.** (2009). Kernel methods in Computer-Aided Constructive Drug Design, Ph.D. dissertation, David R. Cheriton School of Computer Science, University of Waterloo.

Presentations:

- 2015, Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium, Saskatoon, SK, Canada. "Cost-effectiveness of a one-time national hepatitis C screening program: impact of a selective drug reimbursement policy" Oral presentation.
- 2014, Canadian Agency for Drugs and Technologies in Health, Canadian Drug Expert Committee Meeting, Ottawa, Ontario, Canada. "Economic evaluation of direct-acting antiviral therapy for chronic hepatitis C Genotype 1." Invited presentation
- 2014, The 36th Annual Meeting of the Society for Medical Decision Making, Miami, FL, U.S.A. "Cost-Effectiveness of Screening Hepatitis C in Canada." Poster Presentation.
- 2014, The 36th Annual Meeting of the Society for Medical Decision Making, Miami, FL, U.S.A. "Cost-Effectiveness of Hepatitis B Virus Screening Before Adjuvant Chemotherapy in Patients with Early Stage Breast Cancer." Poster Presentation.
- 2014, American Society of Clinical Oncology (ASCO) Quality Symposium, Boston, MA, U.S.A. "HBV screening before adjuvant chemotherapy in patients with early breast cancer: A cost-effectiveness analysis." Poster Presentation.
- 2013, WHO technical consultation on the use of mathematical modelling for viral hepatitis programme planning, Geneva, Switzerland. "Two potential hepatitis C policy models in Canada." Invited presentation.
- 2013, The 35th Annual Meeting of the Society for Medical Decision Making, Baltimore, MA, U.S.A. "The hepatitis C drug pipeline: Collaboration between academic and HTA agency partners to develop an early economic model." Oral presentation.
- 2013, Public Health Agency of Canada: Hepatitis C Virus: Burden and Screening in Canada Workshop, Ottawa, Ontario, Canada. "Cost-Effectiveness of screening hepatitis C in Canada." Invited presentation.

- 2012, The 34th Annual Meeting of the Society for Medical Decision Making, Phoenix, AZ, U.S.A. "A Parallel Sliding Region Algorithm to Make Agent-based Modeling for Large Scale Simulation." Poster presentation.
- 2011, The International Conference on Advances in Probability and Statistics, Hong Kong, China. "Kernel Alignment Feature Selection for Computational Drug Design." Oral presentation.
- 2011, The 3rd International Conference on Infectious Disease Dynamics, Boston, MA, U.S.A. "Developing a complex agent network model to predict HIV and HCV incidence in Canada." Poster presentation
- 2011, The 33rd Annual Meeting of the Society for Medical Decision Making, Chicago, IL, U.S.A. "Developing a Complex Agent Network Model to Predict HIV and HCV Incidence in Canada." Oral presentation.
- 2011, The 33rd Annual Meeting of the Society for Medical Decision Making, Chicago, IL, U.S.A. "Disease Burden of Chronic Hepatitis B among Immigrants in Canada." Poster presentation.
- 2010, American Association for the Study of Liver Diseases (AASLD) – The liver meeting, Boston, MA, U.S.A. "Cost Effectiveness of Screening Immigrants for Hepatitis B." Poster presentation.
- 2010, The 32nd Annual Meeting of the Society for Medical Decision Making, Toronto, ON, Canada. "Cost Effectiveness of Screening Immigrants for Hepatitis B in Canada." Poster presentation.
- 2010, International Conference on Statistics and Society, Beijing, China. "Generalized Genetic Association Study with Samples of Related Individuals." Oral presentation.
- 2010, Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium, Halifax, NS, Canada. "Cost Effectiveness of Screening Immigrants to Canada for Hepatitis B." Poster presentation.

Research Experience

- **Postdoctoral Fellow,** 2010 – 2011, Department of Health Policy, Management & Evaluation, University of Toronto.
  - Project titled: "Model-based economic evaluation of hepatitis C treatment strategies in individuals co-infected with HIV in Canada".
  - Supervisor: Dr. M. Krahn
- **Postdoctoral Fellow,** 2009 – 2010, Department of Health Policy, Management & Evaluation, University of Toronto.
  - Project titled: "Cost-Effectiveness of Screening Immigrants to Canada for Hepatitis B".
  - Supervisors: Dr. J.E. Heathcote and Dr. M. Krahn
- **Research Assistant,** 2002–2009, School of Computer Science, University of Waterloo.
  - Project titled: "Kernel methods in Computer-Aided Constructive Drug Design".
  - Supervisor: Dr. F. J. Burkowski
- **Research Assistant,** 1999–2000, School of Computer Science, University of Waterloo.
  - Project titled: "QX: A System for Visualizing and Mapping XML with SQL".

Teaching Experience

- **Course Guest Lecturer,** 2013-2015, Leslie Dan Faculty of Pharmacy, University of Toronto
  - Course serve:
    - PHM425: Pharmacy practice research
    - PHM1128H: Introduction to Models and Methods of Research
    - PHM1132: Applied Health Economics
- **Course Tutor,** 2013-2014, Leslie Dan Faculty of Pharmacy, University of Toronto
  - Course serve:
    - PHM213: health economics and pharmacoeconomics
    - HAD5304: clinical decision-making and cost-effectiveness analysis
- **Course Instructor,** 2004 – 2009, School of Computer Science, University of Waterloo.
  - Courses taught:
    - *Introduction to Computer Usage* (winter 2009)
    - *Business Systems Analysis* (summer 2006).
    - *Introduction to Computer Programming* (fall 2004 and summer 2005).
- **Teaching Assistant,** 1999 – 2000, 2002 – 2007, School of Computer Science, University of Waterloo.
  - Distinguished Teaching Assistantship Award, 2002.
  - Served as a teaching assistant for various courses in all undergraduate levels including: *Principles of Computer Science*, *Foundations of Sequential Programs*, *Computer Organization & Design*, *Introduction to Algorithm*, *Business Systems Analysis*, and *Structural Bioinformatics*.

Supervision Experience

- Principal Supervisor
  - Edwin Khoo (research associate), 2014/5 – 2014/10, project: Cost-effectiveness of integrated cervical Cancer prevention strategies in Ontario
- Co-supervisor (Unofficial)
  - Yasmin Saeed (MSc), 2014/9 – current, project: Measures of Quality of Life and Utility among Patients with Chronic Hepatitis C Virus Infection
  - Hong-ah Tu (post-doctorate), 2012/5 – 2013/5, project: Cost-Effectiveness of Screening Hepatitis C in Canada
- Academic Advisor
  - Hooman Zangneh (MSc), 2013/9 – current, project: Cost-Effectiveness Analysis of hepatocellular carcinoma screening in patients with hepatitis C related cirrhosis after sustained virological response
  - Ghassan Awadel Karim (MD), 2014/7 – current, project: Cost-effectiveness of interferon-free antivirals compared to standard treatment (Pegylated-interferon with Ribavirin) in Egyptians with Chronic Hepatitis C infection

Other Academic Activities

- Clinical, Social and Administrative Pharmacy Seminars Coordinator 2014 – 2015
- External Mitacs Accelerate grant committee member 2014
- Reviewer for
  - BMC Health Service Research, 2015
  - Hepatology, 2014
  - Pharmacoeconomics, 2014
  - Vaccine, 2013-2014
  - BMC Public Health, 2013
  - Preventing Chronic Disease, 2013, 2014
  - Journal of Hepatology, 2012
  - World Journal of Gastroenterology, 2012
  - Global Health Perspectives, 2012
  - Society for Medical Decision Making Meeting (SMDM) 2011-2013

Academic Awards and Achievements

- 2008 – 2009, University of Waterloo Ph.D. Completion Award
- 2002 – 2003, School of Computer Science Distinguished Teaching Award
- 1999 – 2003, University of Waterloo Graduate Scholarship

Industrial Experience

- **Software Developer,** 2000 – 2001, SWI Systemware Inc., Toronto, Ontario, Canada.

Computer Proficiency

- **Programming Languages:**
  - C/C++, Java, Java Script, Python, Perl, CORBA, Pascal and Visual Basic.
- **Statistical Software:**
  - R, SAS, SPlus, SPSS and Minitab.
- **Decision Making Software**
  - TreeAge Pro, MS-Excel, and Decision Manager.
- **Mathematical Modeling Software:**
  - AnyLogic, Arena, MATLAB, Simulink, and Mathematica.
- **Database:**
  - Oracle, MS SQL Server, Sybase SQL Server, IBM DB2, and MySQL.
- **Operating Systems:**
  - Unix, Linux, MS Windows, Mac OSX, and Sun Solaris.

Professional Memberships

- Society for Medical Decision Making (SMDM)
- American Society of Clinical Oncology (ASCO)
- Institute of Electrical and Electronics Engineers (IEEE)
- Association for Computing Machinery (ACM)
- International Society for Computational Biology (ISCB)

- Molecular Graphics and Modelling Society (MGMS)

REPORT OF THE JOINT COMMITTEE

RELATING TO

FINANCIAL SUFFICIENCY

OF THE 1986-1990 HEPATITIS C TRUST

AS AT DECEMBER 31, 2013

Submitted: March 16, 2015

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1. INTRODUCTION

1. The courts in British Columbia, Ontario and Quebec (Courts) approved The 1986-1990 Hepatitis C Settlement Agreement (Settlement Agreement) in the fall of 1999.[1] They determined on that occasion that while the liabilities under the Settlement Agreement exceeded the settlement amount, the settlement nonetheless was within the envelope of reasonableness.

2. The Settlement Agreement requires that a triennial financial sufficiency assessment be undertaken. At least every third year the Courts must assess whether the assets of the Trust exceed its liabilities and thus determine whether the Trust Fund is financially sufficient in accordance with section 10.01(1)(i) of the Settlement Agreement. The current financial sufficiency assessment was triggered on December 31, 2013.

3. There have been four such triennial financial sufficiency assessments to date (triggered on December 31 of each of 2001, 2004, 2007 and 2010).

4. The Courts have made an order of financial sufficiency on the occasion of each prior triennial financial sufficiency assessment. To date, the Courts have not declared any portion of the money or other assets that are held by the Trustee pursuant to the Settlement Agreement to be actuarially unallocated nor have they exercised their discretion to allocate such funds as is provided for in the orders approving the Settlement Agreement issued in 1999.[2]

2. APPROACH TO ASSESSMENT

5. Section 9.01 of the Settlement Agreement provides for the establishment of a Joint Committee to undertake specified duties as well as duties that the Courts direct. Pursuant to appointments made by the Courts in 1999, 2002 and 2011, the current appointees to the Joint Committee are J. J. Camp, Q.C., Kathryn Podrebarac, Michel Savonitto and Harvey T. Strosberg, Q.C.

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[1] British Columbia Supreme Court Order made October 28, 1999, Ontario Superior Court Order made October 22, 1999, Quebec Superior Court Order made November 19, 1999.

[2] British Columbia Supreme Court Order made October 28, 1999, clause 5(b), Ontario Superior Court Order made October 22, 1999, clause 9(b), Quebec Superior Court Order made November 19, 1999, Schedule F.

6. Section 10.01(1)(i) provides that the Courts will assess the financial sufficiency of the Trust Fund on application of the Joint Committee or any Party to the Settlement Agreement made within 180 days of each third assessment anniversary date.

7. Each prior sufficiency assessment application has happened on the application of the Joint Committee. The record filed by the Joint Committee on each prior assessment included a medical modeling report, an actuarial report from Eckler Ltd. and its predecessors (Eckler) and a report from the Joint Committee providing the assumptions required to calculate the liabilities. Affidavits from medical experts and others have also often formed part of the record filed by the Joint Committee. For several of the most recent sufficiency assessments, the Federal Government has also engaged actuarial experts, Morneau Shepell Inc. and its predecessors (Morneau).

8. The evidentiary record to be filed by the Joint Committee for this financial sufficiency assessement includes a medical model and report, medical evidence, an actuarial report and this report.

9. The Joint Committee report, the medical model and report and the actuarial report are all significantly based on data pertaining to the claims under the Settlement Agreement provided by the Administrator.

10. The Joint Committee provided the non-identifying cohort information and claims data obtained from the Administrator to Eckler, Morneau, the Provincial and Territorial Governments and the medical model working group. This data is the source for a significant number of the assumptions required to complete the financial sufficiency assessment. As such the Joint Committee reviewed the data sets for accuracy, consistency and conformity to the Plans. The inconsistencies and issues with the data that were identified by the Joint Committee and those that were raised by Eckler and/or Morneau were reviewed with the Administrator and resolved in each instance. The Joint Committee catalogued the issues and their solutions and reported to the actuaries on a go forward basis while this aspect of the work was being conducted.

11. What follows is the Joint Committee's report to the Courts pursuant to section 10.01(1)(i) of the Settlement Agreement for the purposes of the financial sufficiency assessment triggered at December 31, 2013.

12. This report summarizes the input the Joint Committee had into the assumptions made by Eckler, provides a summing and reconciliation of benefits paid under the provisions of the Settlement Agreement and the Plans, highlights issues under certain provisions of the Plans that are of significance, and describes the HIV Program under the Settlement Agreement

3. IMPORTANT CONSIDERATIONS FOR ASSESSMENT OF FINANCIAL SUFFICENCY

THE MEDICAL MODEL

13. On settlement approval and for each financial sufficiency assessment conducted under the Settlement Agreement, Dr. Murray Krahn of the University of Toronto has convened a medical model working group (MMWG) of epidemiologists, physicians and statisticians to build (and then refine) an epidemiological model predicting the health outcomes of the class members over time.

14. Advances in treatment in recent years mean that most persons infected with hepatitis C virus (HCV) can receive treatment that is highly effective with fewer side effects than the treatments previously available. These treatment developments were expected to have a significant effect on the medical model and the actuarial outcome. A major aspect of the work to be done to update the medical model would be to incorporate the rapidly changing state of the art in treatment of HCV.

15. Two strategies were developed in this regard: firstly, to request the Administrator to survey claimants who had been treated to determine the antiviral regimen they had been treated with and whether the treatment had been successful (ie. whether they had attained a sustained viral response (SVR) or cure); and, secondly, to have the MMWG survey HCV treating physicians as to treatment patterns presently and anticipated on the horizon.

THE ACTUARIAL PROCESS FOR THE 2013 FINANCIAL SUFFICIENCY ASSESSMENT

16. On the 2010 financial sufficiency assessment (and to a certain extent on the 2007 financial sufficiency assessment), there were differences between the actuaries which were not well understood. The cumulative quantum of these differences on the 2010 assessment was approximately $200 million. These differences are described in the document previously provided to the Courts appended as Appendix A to this report entitled Joint Summary of the Joint Committee and Canada.

17. At the outset of the 2013 assessment, the Joint Committee and the Federal Government agreed on a process to try to eliminate differences between the actuarial reports that were based on technical actuarial modelling not relating to differences in actuarial approach, philosophy or assumptions. The goal was that any differences in outcome would be understood and explainable. For this purpose, Eckler and Morneau were instructed to communicate with each other about their actuarial models, their understanding of the data and medical model and their results as they went. They were encouraged to eliminate technical and modelling outcome differences but to not compromise their independence. They also communicated with the MMWG on the development of the medical model and the medical model report.

THE NOTIONAL ASSETS

18. Although section 10.01(1)(i) directs the assessment of the Trust Fund (the assets held by the Trustee), the actuarial assessment includes consideration of the Trust as a whole. The Trust includes, in addition to the invested assets contributed by the Federal Government, the notional assets[3] which are the obligations of the Provincial and Territorial Governments to pay their 3/11ths share of liabilities as they arise subject to the maximum possible payout. The Joint Committee instructed Eckler to value both the invested assets and the notional assets because the projected liabilities include the obligations of all governments.

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[3] Approximately $162,152,000 at December 31, 2013.

ESTIMATING FINAL COHORT SIZE

19. The size of the cohort of primarily infected persons who would make a timely claim and ultimately be approved for payment under the Transfused HCV Plan and the Hemophiliac HCV Plan (Plans) has been a critical factor in assessing sufficiency from the beginning. A number of considerations come into play in this determination.

20. At the time of the approvals of the Settlement Agreement, the maximum size of the primarily infected hemophiliac cohort entitled to make a claim and ultimately be approved under the Hemophiliac HCV Plan was thought to be essentially known based on the available medical evidence. The criterion for approval of an infected hemophiliac person under the Hemophiliac HCV Plan is satisfied simply by proof of receipt of blood in the period January 1, 1986 to June 30, 1990. Because virtually all of the potential hemophiliac class members who received blood were identified with a hemophiliac treatment centre, the potential maximum cohort of infected hemophiliac persons was estimated at 1645 persons (355 of whom died prior to January 1, 1999).

21. However, at the time of the approvals, the maximum size of the primarily infected transfused cohort entitled to make a claim and ultimately be approved under the Transfused HCV Plan was not known. The criterion for approval of infected persons under the Transfused HCV Plan is proof that they were infected with HCV for the first time by blood received in the class period. Only some of the Provinces and Territories took the step of looking back and identifying those persons who were transfused with blood in the relevant period and encouraging them to be tested. Moreover, because infected persons would not necessarily experience significant symptoms for many years or even decades, a significant percentage of the cohort were yet to be diagnosed. Based upon epidemiological estimates and medical modeling, the maximum cohort of infected transfused persons was first estimated at 8,180 (76 of whom died as a result of HCV prior to January 1, 1999).

22. Over time, the actual claims experience under the Plans has played an increasingly valuable role in estimating the cohort of claimants who will make a timely claim and ultimately be approved under the Plans. The cohort estimates developed on the various prior sufficiency assessments have taken into consideration the number of claims made and approved, the number

of claims made that were in process, the number of claims made which were not being actively pursued and were therefore archived by the administrator, the rate at which claims were made over years and month to month, and the denial rate for claims made. These factors must still be considered because a portion of the cohort is still unknown but, because the first claims deadline has now passed, the uncertainty surrounding cohort size is a much less significant factor today than in prior years.

HEALTH CANADA DENIALS

23. There is a category of denials called Health Canada Negative denials (HCN denials) which, on occasion, occur subsequent to a transfused claim having been approved in the first instance. The court approved traceback protocol (the process by which it is determined if a transfused claimant's infection with HCV was as a result of receipt of blood from an HCV positive donor during the class period) provides that a transfused primarily infected claimant who has an inconclusive traceback after six months is approved under the Transfused HCV Plan subject to future disqualification should the ongoing Health Canada traceback subsequently produce evidence that the claimant was not infected by blood for the first time in the class period. In the event of an HCN denial, the claimant receives no further compensation but is not required to repay any benefits received between initial approval and HCN denial (section 7.05).

24. To date, 99 persons approved and paid compensation have received an HCN denial and are no longer eligible for compensation. A further 8 persons approved but not yet paid compensation at the time their ineligible status became known have been denied compensation based on an HCN denial. Accordingly, the cohort of known transfused primarily infected persons has been reduced by 107 to account for the HCN denials.

THE PASSING OF THE FIRST CLAIM DEADLINE

25. The Plans provide that claims be made before a first claims deadline of June 30, 2010, subject to certain listed exceptions (sections 3.07 Hemophiliac HCV Plan and 3.08 Transfused HCV Plan).

26. Subsequent to the 2010 sufficiency assessment, the Courts approved two protocols which govern the making of claims post June 30, 2010 under these exceptions (CAP1 and CAP2)[4]. By December 31, 2013, 65 persons had claimed under CAP1 and 9 persons had claimed under CAP2. In addition, 60 further claims have been received under these CAPs since this financial sufficiency assessment was triggered.

THE KNOWN COHORTS

27. The approved transfused infected cohort as at December 31, 2013 is 3,924. It is comprised of 3,740 claimants who are alive or who died after January 1, 1999 and 184 claimants who died before January 1, 1999.

28. The approved hemophiliac infected cohort as at December 31, 2013 is 1,359. It is comprised of 1,058 claimants who are alive or who died after January 1, 1999 and 301 claimants who died before January 1, 1999.

THE UNKNOWN COHORT

29. There is still an unknown cohort component which must be accounted for in any financial sufficiency assessment. It is comprised of those claimants whose claims are in process and therefore may or may not go on to become approved and those claimants who have not yet come forward to make a claim under the Plans. The Joint Committee has directed Eckler to estimate the unknown cohort taking into account only those claims which are in process and those claims which will come forward under CAP1 or CAP2 discussed in paragraph 26 above.

30. Subsequent to the 2010 sufficiency assessment, the Courts heard applications brought by Class Counsel to approve a third protocol permitting claims to be made after the June 30, 2010 first claims deadline (CAP3) in those cases where the administrator was satisfied with the reason provided for the claim not having been submitted prior to the deadline. The British Columbia application was dismissed. The Ontario application was approved contingent upon there being a

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[4] Recent HCV Diagnosis Exception to the June 30, 2010 First Claims Deadline Protocol (CAP1) and Issuance of Initial Claims Packages after the June 30, 2010 First Claims Deadline Protocol (CAP2), as amended October 2014.

future declaration of actuarially unallocated assets. The Quebec application was dismissed as premature.

31. Because the decisions of the Courts were not without material differences as required by section 10.01(2) of the Settlement Agreement, the proposed CAP3 did not take effect. The Joint Committee believes that these decisions did not foreclose a renewed request for approval of a late claims protocol in the event the Courts make a declaration identifying actuarially unallocated assets. Accordingly, the Joint Committee instructed Eckler to provide a separate sensitivity analysis for this eventuality.

32. The administrator has recorded 151 infected persons and 76 family members seeking to make claims subsequent to June 30, 2010, who are not covered by the exceptions in CAP1 or CAP2 whose claims could be considered when and if the Courts are satisfied that there are actuarially unallocated assets and if the Courts permit a late claims protocol.

REQUIRED CAPITAL

33. With the main window for new claimants to come forward closed as at June 30, 2010, the Joint Committee sought Eckler's advice on the amount of additional assets in excess of projected liabilities which are required to ensure the soundness of the Plans' operation and to protect the class members against the risk that the medical modelling projections, the data analysis and/or assumptions, and/or the actuarial projections under-estimate the liabilities or overestimate the assets. Eckler has applied established actuarial principles to calculate the amount of assets over and above those necessary to meet the liabilities which are needed to protect the class members from future major adverse experience or catastrophe.

4. PAYMENTS MADE UNDER THE PLANS – 2011 TO 2013

34. The Settlement Agreement provides for a variety of compensation payments responsive to claims made by the class members under the following three compensation plans:

(a) the Transfused HCV Plan;

(b) the Hemophiliac HCV Plan; and

(c) the HIV Secondarily Infected Program (HIV Program) discussed in section 7 below.

35. The Plans provide for compensation to be paid to approved HCV claimants for a variety of losses. The types and amounts of the losses to be paid to claimants are in large measure tied to their progression through the disease levels over time. Many of the compensation amounts are indexed by inflation for each year.

36. The Plans, in the first instance, provided for limitations or holdbacks on certain payments pending periodic reassessment of the Courts and a decision to amend or remove the limitations (section 7.03). Section 10.01(1)(i) of the Settlement Agreement requires the Courts to consider whether any of the restrictions or holdbacks on payments in the Plans should be removed in whole or in part. The extent to which these limitations or holdbacks have been amended or removed is discussed in the paragraphs that follow.

37. As part of the process of analyzing and verifying the claims data, the Joint Committee has summed and reconciled the claims payment data for 2011 to 2013 under the various payment provisions of the Plans.

38. The results of this analysis are set out in paragraphs 39 to 67.

FIXED PAYMENTS – SECTION 4.01 OF THE PLAN

39. The Plans provide that approved infected claimants who are alive and the estates of persons who died after January 1, 1999 (DA9s) without collecting payments prior to their death receive the fixed payments available for their current disease levels and all lower disease levels. The fixed payments made in 2011 to 2013 for the various disease levels were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.01(1)(a) Level 1 Fixed Payment	$10,000	(64) $826,535.42	(19) $249,023.12	(43) $573,490.57	$1,649,049.11
4.01(1)(b) Level 2 Fixed Payment	$20,000	(45) $1,172,469.62	(18) $471,833.10	(74) $986,937.26	$2,631,239.98
4.01(1)(b) Level 2 Holdback	$5,000	Nil	Nil	Nil	Nil

4.01(1)(c) Level 3 Fixed Payment	$30,000	(38) $1,491,075.69	(31) $1,218,902.33	(45) $1,800,494.10	$4,510,472.12
4.01(1)(d) Level 5 Fixed Payment	$65,000	(29) $2,485,126.20	(14) $1,192,689.40	(20) $1,733,809.00	$5,411,624.60
4.01(1)(e) Level 6 Fixed Payment	$100,000	(24) $3,186,059.25	(13) $1,703,841.88	(11) $1,467,069.12	$6,356,970.25

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.01(1)(a) Level 1 Fixed Payment	$10,000	(4) $50,976.96	(1) $13,106.48	(1) $13,336.99	$77,420.43
4.01(1)(b) Level 2 Fixed Payment	$20,000	(2) $50,976.94	(1) $26,212.95	(1) $26,673.98	$103,863.87
4.01(1)(b) Level 2 Holdback	$5,000	Nil	Nil	Nil	Nil
4.01(1)(c) Level 3 Fixed Payment	$30,000	(5) $191,163.55	(3) $117,958.29	(4) $160,043.92	$469,165.76
4.01(1)(d) Level 5 Fixed Payment	$65,000	(9) $745,537.86	(4) $340,768.40	(5) $433,452.25	$1,519,758.51
4.01(1)(e) Level 6 Fixed Payment	$100,000	(7) $892,096.59	(6) $786,388.56	(4) $533,479.68	$2,211,964.83

40. Initially, $5,000 of the $20,000 disease level 2 fixed payment (1999 dollars) was deferred as a result of one of the limitations or holdbacks imposed by the Plans. Following the 2001 sufficiency assessment the limitation on the level 2 payment was removed by the Courts and the holdback which had accrued was paid out to claimants approved to that point with interest. Thereafter, new claims approved at disease level 2 were paid the fixed payment in full.

LEVEL 3 LOSS OF INCOME SERVICES IN LIEU OF LEVEL 3 FIXED PAYMENT AND LOSS OF INCOME/SERVICES – SECTIONS 4.01(3), 4.02, 40.03 OF THE PLAN

41. The Plans provide that approved infected claimants at disease level 3 who are alive and the estates of DA9s with unpaid pre-death losses may elect to waive the $30,000 fixed payment (1999 dollars), provided the infected person is at least 80% disabled, and claim instead their net after-tax loss of income or for their loss of services experienced in the home.

42. The Plans also provide that approved infected claimants at disease level 4 or above who are alive and the estates of DA9s with unpaid pre-death losses may claim compensation for their net after-tax loss of income or for their loss of services experienced in the home.

43. Eckler requested that the Joint Committee provide certain income and service loss calculations from the claims data. The calculations provided are as follows:

The claims experience shows that:

(a) 38% (350 claimants/898 claimants) of levels 3 to 6 alive or DA9 primarily infected claimants who were paid loss of income/services on average received 4.95 years of payments (1,735 years/350 claimants) within the 10 year period from their date of transfusion or receipt of blood products (for DA9 claimants up to their year of death);

(b) 71.93% (646 claimants/898 claimants) of levels 3 to 6 alive and DA9 primarily infected claimants who took loss of income/services were paid on average 5.91 years (3,820 years/646 claimants) of past loss of income/services payments where past loss of income/services means the years preceding a claimant's approval year (for DA9 claimants up to their year of death);

(c) the average number of years of past loss of support/services paid for transfused primarily infected DB9 deaths caused by HCV is 7.94 years (683 years/86 claimants) (where past loss means from the year of death to the year preceding the approval year); and

(d) the average number of years of past loss of support/services paid for hemophiliac primarily infected DB9 deaths caused by HCV is 9.02 years (740 years/82 claimants) (where past loss means from the year of death to the year preceding the approval year).

44. Claimants entitled to loss of income or loss of services payments have been paid from the beginning of the year of disability to December 31, 2012. The losses for these types of claims are paid one year in arrears because income tax information is required to process entitlement.

45. The payments made for loss of income and loss of services in 2011 to 2013 (for years 2010 to 2012) were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.01(3)/4.02 Loss of Income	Based on prior earned income	(67) $3,319,728.17	(69) $2,807,732.66	(70) $3,002,437.88	$9,129,898.71
4.01(3)/4.03 Loss of Services	$12/hour up to $240/week	(179) $3,976,365.52	(182) $5,289,620.92	(185) $4,268,156.57	$13,534,143.01

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.01(3)/4.02 Loss of Income	Based on prior earned income	(47) $3,263,961.91	(43) $3,390,686.28	(45) $3,637,546.05	$10,292,194.24
4.01(3)/4.03(2) Loss of Services	$12/hour up to $240/week	(112) $2,175,562.99	(107) $1,753,208.17	(108) $1,921,041.64	$5,849,812.80

46. Until 2004, as a result of the required limitations or holdbacks, the Plans paid only 70% of loss of income based on pre-claim gross income of up to $75,000 (1999 dollars). For approved loss of income claims before 2004, 30% of the loss and any loss based on pre-claim gross income above the $75,000 maximum accrued to the claimant pending a decision by the Courts that these limitations be amended or removed.

47. In 2004, the 70% limitation on payment of loss of income claims was removed and the limitation on pre-claim gross income was increased to a maximum of $300,000 (1999 dollars). All accrued loss of income payments triggered by eliminating the 70% payment restriction on income loss and by raising the $75,000 limitation to $300,000 were paid out with interest. Thereafter, approved loss of income claimants were paid 100% of their loss of income based upon a calculation which permitted pre-claim gross income of up to $300,000.

48. In 2008, the Courts raised the limitation on pre-claim gross income which could be used in the calculation of a loss of income claim to a maximum of $2.3 million (1999 dollars) with the proviso that any claim calculated on pre-claim gross income in excess of $300,000 (1999 dollars) required express approval from the Court with jurisdiction prior to its payment.

49. The Courts have approved ongoing payment for 4 claimants with loss of income claims based on pre-claim gross income in excess of $300,000 (including prior year and ongoing

claims). One such claim ended in 2005, the second ended after the 2010 payment, and the other two claims are ongoing to 2024 and 2034,[5] respectively.

COSTS OF CARE – SECTION 4.04 OF THE PLANS

50. The Plans provide that approved infected claimants at disease level 6 who are alive and the estates of level 6 DA9s with unpaid pre-death losses are entitled to claim up to $50,000 (1999 dollars) per year for costs of care, including services provided by family members that are not already compensated under the loss of services provisions.

51. At the beginning of 2010, the standard operating procedure for claiming costs of care was modified by the Courts to improve the administrative process and to increase rates payable for certain services.

52. The payments made for costs of care in 2011 to 2013 were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.04 Costs of Care	Up to $50,000	(35) $910,575.48	(30) $1,119,560.90	(35) $1,806,961.29	$3,837,097.67

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.04 Costs of Care	Up to $50,000	(21) $593,140.27	(20) $705,490.52	(18) $732,463.08	$2,031,093.87

COMPENSABLE HCV DRUG THERAPY – SECTION 4.05 OF THE PLANS

53. The Plans and the Court approved protocol for compensable HCV drug therapy provide for a payment of $1,000 per month (1999 dollars) for each month an approved infected claimant at disease levels 3 to 6 underwent a treatment regimen that included either interferon or ribavirin or both or a DA9 claimant at those levels underwent such treatment prior to his or her death. The payments made for compensable HCV drug therapy in 2011 to 2013 were as follows:

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[5] The loss of income payments to these claimants were $1,497,000 (2012) and $290,447 (2013), respectively (despite a high pre-claim net income, the later claimant remains in the work force to this point and has a correspondingly high post-claim net income offset).

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.05 HCV Compensable Drug Therapy	$1,000/month	(52) $526,335.46	(41) $398,437.60	(68) $688,189.20	$1,612,962.26

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.05 HCV Compensable Drug Therapy	$1,000/month	(14) $175,869.96	(16) $162,520.60	(30) $385,439.30	$723,829.86

54. These monthly payments are provided to people who undergo these treatments to compensate for the adverse side effects generally associated with interferon and/or ribavirin (and/or such other treatments as may be approved by the Courts). As is more fully explained in the medical evidence, medical modeling and actuarial reports, several new drugs with varying regimens and varying levels of side effects have recently become available for treatment of the HCV virus. In some cases, these treatments do not include interferon or ribavirin and so do not qualify for the compensable HCV drug therapy payment unless the Courts make orders that they be added to the list of eligible treatments. Applications have not yet been made to the Courts seeking coverage for any of the new treatments as Compensable HCV drug therapy pending more complete medical information. Accordingly, the impact of these new treatment regimens on payments under this head of compensation is not yet clear.

UNINSURED TREATMENT AND MEDICATION – SECTION 4.06 OF THE PLANS

55. The Plans (section 1.01 definition and section 4.05) reimburse the cost of uninsured generally accepted treatment and medication expenses incurred in the treatment or management of HCV for approved infected claimants who are alive and the estates of DA9s with unpaid pre-death expenses. These claims may include the HCV drug therapy regimens and many other medications and treatments. The payments made for uninsured treatment and medication in 2011 to 2013 were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.06 Uninsured Treatment & Medication	Reimbursed expenses	(97) $188,335.04	(87) $354,754.20	(99) $376,152.96	$919,242.20

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.06 Uninsured Treatment & Medication	Reimbursed expenses	(53) $206,236.31	(51) $290,825.48	(64) $294,289.09	$791,350.88

56. The cost of reimbursing uninsured treatment and medication expenses may fluctuate significantly in the future as several factors impact future costs. As outlined more fully in the medical evidence and actuarial reports, the cost of the new drug therapy treatments which have recently become available are significant and the amounts and the timing of coverage by provincial and/or private drug plans cannot be predicted. It is predicted that the number of persons eligible to take the new treatments will increase which will increase the outlay under these provisions of the Plans in the near future. The cost of medications developed in the future for the treatment of HCV and/or newly diagnosed HCV related diseases and/or conditions is another unknown. However, if the new drug therapy treatment regimens prove to be successful, as predicted, the number of class members who attain a sustained viral response (considered as cured) will be high and their future treatment needs and these future payments under the Plans will be eliminated or reduced.

OUT-OF-POCKET EXPENSES – SECION 4.07 OF THE PLANS

57. The Plans provide for reimbursement at all disease levels for uninsured out-of-pocket expenses incurred as a result of HCV infection to approved infected claimants who are alive and to the estates of DA9 infected claimants with unpaid pre-death expenses. The payments made for out-of-pocket expenses in 2011 to 2013 were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.07 Out-of-Pockets	Reimbursed expenses	(168) $271,018.99	(149) $221,372.41	(158) $313,582.99	$805,974.39

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
4.07 Out-of-Pockets	Reimbursed expenses	(90) $203,264.81	(99) $164,206.47	(98) $184,049.47	$551,520.75

58. The court approved protocol for uninsured out-of-pocket expenses was modified by the Courts at the beginning of 2011 to make claiming for out-of-pocket expenses simpler for claimants.

59. Although the medical evidence is that follow up care is needed for some persons who attain a sustained viral response following treatment, the new drug therapy treatment regimens will also have a favourable impact on these future out-of-pocket cost provisions over the long term.

HIV SECONDARILY INFECTED - SECTIONS 4.08 OF THE TRANSFUSED HCV PLAN OR 4.08(1) OF THE HEMOPHILIAC HCV PLAN AND 5.01(3) AND 5.02(2) OF THE PLANS

60. As has been previously noted, the Settlement Agreement establishes the HIV Program to provide compensation to persons secondarily infected with HIV. The HIV Program provides for an unindexed lump sum payment of $240,000 to approved claimants.

61. The Plans also provide for the payment of provable benefits above the threshold of $240,000 (not indexed) to HCV infected persons who are also HIV secondarily infected persons eligible for compensation under the HIV Program. Similar provisions apply to claims by the estates, dependants and family members of such co-infected claimants. There have been no payments made under these provisions to date.

DEATH CLAIMS FOR PERSON WHO DIED PRIOR TO JANUARY 1, 1999 (DB9s) – SECTIONS 5.01, 6.01 AND 6.02 OF THE PLANS

62. The Plans provide, with one exception discussed in paragraphs 66 and 67 below, that HCV must have caused the death of an HCV infected claimant who died prior to January 1, 1999 (DB9) in order for benefits to be payable. In all issues of causation under the Settlement Agreement and the Plans, the Joint Committee has instructed Eckler that the legal definition of

causation which was the law at the time the Settlement Agreement was negotiated and approved, that is material contribution, is the standard that the Administrator uses.

63. The estate, the family members and dependants of an approved DB9 whose death was caused by HCV may either claim:

(a) uninsured funeral expenses of up to $5,000 (1999 dollars), an estate payment of $50,000 (1999 dollars), amounts for loss of support/services for dependants during the deceased's life expectancy, and fixed amounts for loss of guidance, care and companionship for the family members (the $50,000 Option); or

(b) uninsured funeral expenses of up to $5,000 (1999 dollars) and a one-time all inclusive payment of $120,000 (1999 dollars) to be divided among them in settlement of all claims (the $120,000 Option).

64. The payments made relating to these DB9 claims in 2011 to 2013 were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
5.01(1) DB9 Funeral	Up to $5,000	(5) $21,699.06	Nil	Nil	$21,699.06
5.01(1) DB9 $50,000 Option	$50,000	(2) $127,442.38	Nil	(1) $66,684.96	$194,127.34
5.01(2) DB9 $120,000 Option	$120,000	(2) $305,861.81	Nil	Nil	$305,861.81
6.01(1) DB9 - Loss of Support	Based on prior earned income	(15) $599,162.04	(12) $260,379.81	(11) $231,270.94	$1,090,812.80
6.01(2) DB9 – Loss of Services	$12/hr up to $240/week	(44) $897,857.09	(44) $812,665.15	(37) $870,250.28	$2,580,772.52
6.02(a) DB9 FM- Spouse	$25,000	(2) $63,721.18	Nil	(1) $33,342.48	$97,063.66
6.02(b) DB9 FM-Child < 21	$15,000	Nil	Nil	Nil	Nil
6.02(c), (d), (e) DB9 FM-Child >21, Sibling, Parent	$5,000	(6) $38,232.72	(5) $32,766.20	(2) $13,337.00	$84,335.92
6.02(f), (g) DB9 FM – Grandparent, Grandchild	$500	(4) $2,548.84	(17) $11,140.44	(1) $666.85	$14,356.13

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
5.01(1) DB9 Funeral	Up to $5,000	Nil	Nil	Nil	Nil
5.01(1) DB9 $50,000 Option	$50,000	Nil	Nil	Nil	Nil
5.01(2) DB9 $120,000 Option	$120,000	Nil	Nil	Nil	Nil
6.01(1) DB9 - Loss of Support	Based on prior earned income	(25) $425,257.46	(39) $992,197.88	(26) $405,226.35	$1,822,681.69

6.01(2) DB9 – Loss of Services	$12/hr up to $240/week	(61) $726,856.26	(52) $662,496.32	(51) $668,862.24	$2,058,214.82
6.02(a) DB9 - FM- Spouse	$25,000	Nil	Nil	(1) $33,342.48	$33,342.48
6.02(b) DB9 - FM-Child < 21	$15,000	Nil	Nil	Nil	Nil
6.02(c), (d), (e) DB9 – FM - Child >21, Sibling, Parent	$5,000	Nil	Nil	Nil	Nil
6.02(f), (g) DB9 - FM – Grandparent or Grandchild	$500	Nil	Nil	Nil	Nil

DEATH CLAIMS FOR PERSONS WHO DIED AFTER JANUARY 1, 1999 (DA9s) – SECTIONS 5.02, 6.01 AND 6.02 OF THE PLANS

65. The Plans provide that the estate of a DA9 may claim all unpaid compensation which the deceased could have claimed prior to death. In addition, if the death was caused by HCV, the estate may claim for uninsured funeral expenses of up to $5,000 (1999 dollars), the dependants may claim for loss of support/services during the deceased's life expectancy, and the family members may claim fixed amounts for loss of guidance, care and companionship. The payments made relating to these DA9 claims in 2011 to 2013 were as follows:

TRANSFUSED HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	Total Paid 2011-2013
5.02(1) DA9 Funeral	Up to $5,000	(29) $118,044.99	(15) $55,787.88	(13) $64,181.45	$238,014.32
6.0191) DA9 – Loss of Support	Based on prior earned income	(24) $431,870.31	(31) $842,053.04	(23) $490,664.80	$1,764,588.15
6.01(2) DA9 – Loss of Services	$12/hr up to $240/week	(177) $2,404,822.15	(168) $2,630,889.70	(161) $2,388,490.27	$7,424,202.12
6.02(a) DA9 FM-Spouse	$25,000	(18) $573,490.62	(12) $393,194.28	(10) $333,424.80	$1,300,109.70
6.02(b) DA9 FM-Child<21	$15,000	(2) $38,232.72	(2) $39,319.42	Nil	$77,552.14
6.02(c),(d),(e) DA9 FM-Child>21, Sibling, Parent	$5,000	(111) $707,201.04	(80) $524,259.20	(8) $533,480.00	$1,764,940.24
6.02(f),(g) DA9 FM-Grandparent, Grandchild	$500	(95) $60,534.95	(60) $38,663.88	(74) $49,346.90	$148,545.73

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amount	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
5.02(1) DA9 Funeral	Up to $5,000	(4) $18,614.33	(7) $36,845.91	(6) $34,388.61	$89,848.85
6.0191) DA9 – Loss of Support	Based on prior earned	(41) $1,666,324.30	(22) $375,679.25	(35) $913,512.49	$2,955,516.04

	income				
6.01(2) DA9 – Loss of Services	$12/hr up to $240/week	(64) $874,331.85	(58) $662,862.59	(65) $757,433.79	$2,294,628.23
6.02(a) DA9 FM – Spouse	$25,000	(4) $127,442.36	(4) $131,064.76	(5) $166,712.40	$425,219.52
6.02(b) DA9 FM – Child < 21	$15,000	(10) $19,116.36	(4) $78,638.84	(4) $80,021.96	$177,777.16
6.02(c),(d),(e) DA9 FM – Child >21, Sibling, Parent	$5,000	(30) $203,907.84	(46) $301,449.04	(31) $206,723.50	$712,080.38
6.02(f),(g) DA9 FM –Grandparent or Grandchild	$500	(20) $13,381.41	(30) $19,659.60	(8) $5,334.80	$38,375.81

CO-INFECTED ELECTIONS – SECTIONS 4.08(2) AND 5.01(4) OF THE HEMOPHILIAC HCV PLAN

66. The Hemophiliac HCV Plan provides a compensation scheme that is identical to the Transfused HCV Plan in most respects and, in addition, provides that:

(a) alive primarily infected claimants also infected with HIV may elect a $50,000 (1999 dollars) payment in satisfaction of all claims including those of family members and dependants; or

(b) the estate, family members and dependants of primarily infected DB9s also infected with HIV may elect a $72,000 (1999 dollars) payment to be divided among them in satisfaction of all claims without proof of HCV as the cause of death.

67. The payments made for co-infected elections in 2011 to 2013 were as follows:

HEMOPHILIAC HCV PLAN

Type of Payment	1999 Amounts	Paid 2011 (Indexed)	Paid 2012 (Indexed)	Paid 2013 (Indexed)	TOTAL Paid 2011-2013
4.08(2) Alive HIV Co-Infected Option	$50,000	(1) $63,721.19	Nil	(2) $133,369.92	$197,091.11
5.01(4) DB9 HIV Co-infected Option	$72,000	(1) $91,758.49	Nil	Nil	$91,758.49

5. RECONCILIATION OF PAYMENTS MADE UNDER THE PLANS THROUGH 2013

68. As part of the process of testing and analyzing the claims data, the Joint Committee has also reconciled the payments made under each provision of the Plans as at the trigger date for

each triennial sufficiency assessment throughout the claims administration to December 31, 2013. These reconciliations were provided to the actuaries for their use in the financial sufficiency assessment. The reconciliations are appended as Appendix B.

6. DEVELOPING ASSUMPTIONS FOR FEES AND EXPENSES RELATING TO THE PLANS

69. On previous triennial sufficiency assessments, the assumptions relating to the fees and expenses payable for the ongoing operations and administration under the Plans have been calculated for a fixed number of years and then reduced to zero. This somewhat abrupt notional cessation of administrative costs was assumed because expenses have a progressively smaller present value, due to discounting, as one moves further out along the time horizon.

70. For the 2013 sufficiency assessment, the Joint Committee conferred with Eckler on whether this methodology sufficiently accounted for further expenses under the Plans given the overriding approach that the Plans will continue as a going-concern until all benefits due to claimants have been paid. As a result, Eckler has developed the expense assumptions for the 2013 sufficiency assessment by projecting them out over the life of the going-concern payments but reducing the expenses going forward in proportion to the projected number of claimants alive at these future dates.

71. In order to project these expenses, the Joint Committee provided Eckler with information on past expenses and current service provider budgets in the near term and consulted with them on anticipated expenses in future years.

7. HIV PROGRAM AND RELATED ASSUMPTIONS

72. The HIV Program established under the Settlement Agreement provides for:

(a) payment of up to 240 payments of $240,000 (not indexed) to approved persons secondarily infected with HIV; and

(b) payment of administrative expenses of up to $2 million dollars.

The HIV Program has no claims deadline.

73. A total of 89 claims have been paid under the HIV Program, two of which have been paid since the 2010 sufficiency assessment.

74. Seven claims are currently registered under the HIV Program, including three claims which have been in process for a number of years and three registrants who have not submitted their completed claims package.

75. A separate budget for expenses relating to the HIV Program is no longer maintained. Any costs associated with administering the HIV Program are covered by the expenses budgeted for the Plans.

76. For the 2013 financial sufficiency assessment, the Joint Committee instructed Eckler to assume:

(a) five additional HIV Program payments, each in the amount of $240,000, occurring every third year starting in 2014; and

(b) that no additional administrative expenses will be paid relating to the HIV Program.

8. OUTCOME OF THE 2013 FINANCIAL SUFFICIENCY ASSESSMENT

77. Although the Eckler actuarial model and the Morneau actuarial model are different in structure and in approach, the actuaries have agreed on the development of the major assumptions and used the same medical model. The Joint Committee understands the differences in results of the actuarial models are very small and that both conclude that the assets exceed the liabilities, that a buffer is appropriate, and that after the buffer the assets still exceed the liabilities.

APPENDIX A

1986-1990 HEPATITIS C SETTLEMENT AGREEMENT

2010 FINANCIAL SUFFICIENCY REVIEW

JOINT SUMMARY OF THE JOINT COMMITTEE AND CANADA

1. Section 10.01(1)(i) of the 1986-1990 Hepatitis C Settlement Agreement (the "Agreement") requires that an application be made every three years to assess the financial sufficiency of the Trust Fund.

2. To date, in each of the preceding triennial fund sufficiency hearings, the Courts have issued orders that the Trust Fund is financially sufficient.

3. The assets and liabilities pertaining to the Agreement were assessed by actuaries for the Joint Committee (by Eckler Ltd.) and for Canada (by Morneau Shepell) as at December 31, 2010.

4. Originally, the parties anticipated that an application would be made to the Courts in 2012 to ascertain the range of any surplus that could be allocated pursuant to the provisions of the orders issued by the Courts at the time the original settlement terms were approved by the Courts.

5. Several issues have arisen which makes the identification of a any surplus for allocation problematic. Some of these larger issues are as follows:

   (a) the difference between the medical model's treatment of HCV death causation and the administrative treatment of that issue. This issue ("Excess HCV Death Causation") over the probable lifetime of the Plans has a probable adverse impact on the Trust Fund by increasing liabilities by $91 million (Eckler Ltd.) to $133 million (Morneau Shepell);

   (b) subsequent to the Eckler Report and during the preparation of the Morneau Report, protocols were proposed pertaining class members who first attempted to make claims after the June 30, 2010 first claims deadline (loosely described as "Late Claims"). Two of these protocols were approved by the Courts without any objection by the FPT Governments and the third of these protocols will be the subject of an application to the Courts. The liabilities associated with these three protocols have been actuarially assessed by Eckler Ltd. at $90 million;

   (c) in the last several months new drugs are entering the field of HCV treatment and the first indications are that these drugs could have a very powerful curative effect for those HCV sufferers who are medically eligible to be prescribed them. These drugs are expensive (approximately $45,000 for a regimen of three months treatment) but if a substantial number of Class Members are cured, these drugs could have a very significant impact of reducing future liabilities. At

the same time, costs related to compensation of uninsured medication will increase to the extent the drugs are not covered by the provincial drug plans;

(d) there are different approaches to incorporating disease progression into the actuarial models employed by Eckler Ltd. and Morneau Shepell. The difference between the approaches is in the range of $25 million to $125 million;

(e) there are substantial differences of opinion between Eckler Ltd. and Morneau Shepell pertaining to margins for adverse deviation and provisions for adverse deviation ("MfAd" and "PfAD"). The difference in liabilities between these approaches is cumulatively in excess of $100 million; and

(f) there are substantial differences of opinion between Eckler Ltd. and Morneau Shepell pertaining to the approach to calculating a buffer and the quantum of the buffer before any suplus can be identified for allocation. These differences in buffer assessment and calculation are approximately $70-$85 million, subject to the resolution of the Late Claims issue.

6. It is proposed by the Joint Committee and Canada that these differences be ironed out as much as possible by the parties and their respective actuaries before any application is brought to identify any surplus available for allocation and before any application is brought to allocate any surplus. At this time, the parties propose to obtain the same order that the Courts have issued to date, namely, that the Trust Fund is financially sufficient.

APPENDIX B
RECONCILIATION OF PAYMENTS UNDER THE 1986-1990 TRANSFUSED HCV PLAN 2000 - 2013

Type of Payment	1999 Amount	Paid 2000-2010	Paid 2011	Paid 2012	Paid 2013	Total Paid 2011-2013	Total Paid 2000-2013
4.01(1)(a) Level 1 Fixed Payment	$10,000	$39,813,122.07[1]	$826,535.42	$249,023.12	$573,490.57	$1,649,049.11	$41,462,171.18
4.01(1)(b) Level 2 Fixed Payment[2]	$15,000/$20,000	$55,173,442.91	$1,172,469.62	$471,833.10	$986,937.26	$2,631,239.98	$57,804,682.89
4.01(1)(b) Level 2 Holdback[3]	$5,000	$10,685,054.70	Nil	Nil	Nil	Nil	$10,685,054.70
4.01(1)(c) Level 3 Fixed Payment	$30,000	$56,182,436.97	$1,491,075.69	$1,218,902.33	$1,800,494.10	$4,510,472.12	$60,692,909.09
4.01(1)(d) Level 5 Fixed Payment	$65,000	$46,601,787.28	$2,485,126.20	$1,192,689.40	$1,733,809.00	$5,411,624.60	$52,013,411.88
4.01(1)(e) Level 6 Fixed Payment	$100,000	$46,060,311.71	$3,186,059.25	$1,703,841.88	$1,467,069.12	$6,356,970.25	$52,417,281.96
4.02 Loss of Income[4]	N/A	$37,852,663.93	$3,319,728.17	$2,807,732.66	$3,002,437.88	$9,129,898.71	$46,982,562.64
4.03 Loss of Services[5]	$12/hour to $240/week	$49,237,672.56	$3,976,365.52	$5,289,620.92	$4,268,156.57	$13,534,143.01	$62,771,815.57
4.04 Cost of Care	$50,000	$9,857,619.57	$910,575.48	$1,119,560.90	$1,806,961.29	$3,837,097.67	$13,694,717.24
4.05 HCV Drug Therapy per month	$1,000	$11,248,982.92	$526,335.46	$398,437.60	$688,189.20	$1,612,962.26	$12,861,945.18
4.06 Uninsured Treatment & Medication	N/A	$3,438,314.35	$188,335.04	$354,754.20	$376,152.96	$919,242.20	$4,357,556.55
4.07 Out of Pockets	N/A	$3,883,179.14	$271,018.99	$221,372.41	$313,582.99	$805,974.39	$4,689,153.53
5.01(1) DB9 Funeral	$5,000	$549,864.92	$21,699.06	Nil	Nil	$21,699.06	$571,563.98
5.01(1) DB9 Estate	$50,000	$4,999,897.03	$127,442.38	Nil	$66,684.96	$194,127.34	$5,194,024.37
5.01(2) DB9 Option	$120,000	$11,544,957.72[6]	$305,861.81	Nil	Nil	$305,861.81	$11,850,819.53
5.02(1) DA9 Funeral	$5,000	$1,454,806.95	$118,044.99	$55,787.88	$64,181.45	$238,014.32	$1,692,821.27
6.01(1) Loss of Support[7]	N/A	$9,131,721.28	$1,031,032.35	$1,102,432.86	$721,935.74	$2,855,400.95	$11,987,122.23
6.01(2) Loss of Services[7]	$12/hour to $240/week	$29,565,064.61	$3,302,679.24	$3,443,554,.85	$3,258,740.55	$10,004,974.64	$39,570,039.25
6.02(a) DB9 FM- Spouse	$25,000	$2,374,307.16	$63,721.18	Nil	$33,342.48	$97,063.66	$2,471,370.82
6.02(b) DB9 FM-Child < 21	$15,000	$512,582.85	Nil	Nil	Nil	Nil	$512,582.85
6.02(c), (d), (e) DB9 FM- Child >21, Sibling, Parent	$5,000	$2,427,399.00	$38,232.72	$32,766.20	$13,337.00	$84,335.92	$2,511,734.92
6.02(f), (g) DB9 FM – Grandparent, Grandchild	$500	$181,494.55	$2,548.84	$11,140.44	$666.85	$14,356.13	$195,850.68
6.02(a) DA9 FM-Spouse	$25,000	$7,437,111.75	$573,490.62	$393,194.28	$333,424.80	$1,300,109.70	$8,737,221.45
6.02(b) DA9 FM-Child<21	$15,000	$761,168.00	$38,232.72	$39,319.42	Nil	$77,552.14	$838,720.14
6.02(c),(d),(e) DA9 FM-Child>21, Sibling, Parent	$5,000	$10,517,272.52[8]	$707,201.04	$524,259.20	$533,480.00	$1,764,940.24	$12,282,212.76
6.02(f),(g) DA9 FM-Grandparent, Grandchild	$500	$886,500.22	$60,534.95	$38,663.88	$49,346.90	$148,545.73	$1,035,045.95
Total Paid		**$452,378,736.67[9]**	**$24,744,346.74**	**$20,668,887.53**	**$22,092,421.67**	**$67,505,655.94**	**$519,884,392.61**

Subtotal Reconciliation	**$519,884,392.61**	
Less	**1,918,048.75**	**(Adjustments and credits for other provincial HCV programs)**
Total Reconciliation	**$517,966,343.86[10]**	

[1] A payment of $10,904.06 originally shown as made in 2003 was not actually paid until 2011 (Claim No. 170).

[2] Level 2 Fixed Payments were $15,000 until approximately September 2002 when the Courts ordered the Level 2 Holdback removed and the Fixed Payments increased to $20,000.

[3] The Level 2 Holdback (plus interest) was paid to those persons who had received a Level 2 Fixed Payment while the Holdback was in place.

[4] Loss of Income payments under this provision are for alive HCV Infected Persons and for the Estates of HCV Infected Persons who died after January 1, 1999 ("DA9s") where a loss of income incurred prior to death had not already been paid to the HCV Infected Person. Loss of Income payments have been made covering income losses to December 31, 2012. The 2013 payments will be calculated when the claimants provide their 2013 income tax information to the Administrator. These payments also include a Loss of Income payment in the amount of $55,677.26 mistakenly made in 2002 to the Estate of an HCV Infected Person who died before January 1, 1999 ("DB9") (Claim No.1200332). The Fund was repaid for the payment made in error. Because Dependants of DB9s are entitled to claim Loss of Support provided the death was caused by HCV and because the Loss of Income/Loss of Support software computes a Loss of Income for the actual year of death and thereafter converts to a Loss of Support claim for subsequent years, these payments include Loss of Income payments to Estates of DB9s for the year of death in the amount of $474,365.63 including holdbacks where appropriate (Claim Nos.136, 224, 246, 1157, 3007, 13000, 15245, 1000101, 1000125, 1000621, 1200081, 1200299, 1200332, 1400153, 1400453, 1401009, 1401534, 1402675).

[5] Loss of Services payments under this provision are for alive HCV Infected Persons and for the Estates of DA9s where a loss of services was incurred prior to death. Loss of Services payments have been made to December 31, 2012. The 2013 payments are currently being assessed. These payments also include Loss of Services payments in the amount of $419,610.99 mistakenly made to the Estates of DB9s in the years 2001 and 2002 (Claim Nos.941, 1354, 1000377, 1000575, 1200062, 1200332, 1401370, 1401567, 1401772). The Fund was repaid for these payments made in error.

[6] These payments include $128,745.39 paid to a Sibling in 2002 although not properly coded (Claim No. 5129) and payments of $260,898.98 to Family Members although coded as Estate files (Claim Nos. 1400325, 1401625, 1402447, 1402608, 1402644).

[7] Loss of Support/Services payments under these provisions are for Dependants who have suffered a Loss of Support/Services following the death of an HCV Infected Person (either DB9 or DA9) provided the death was caused by HCV. Payments have been made to December 31, 2012. The 2013 payments are currently being assessed.

[8] A payment of $6,267.84 originally shown as made in 2010 was not actually paid until 2011 (Claim No. 19290).

[9] This total has been adjusted to reflect the timing of the payments discussed in footnotes 1 and 8.

[10] This payment reconciliation equals the adjusted totals calculated from the Access and Excel databases provided by the Administrator as at December 31, 2013.

RECONCILIATION OF PAYMENTS UNDER THE 1986 – 1990 HEMOPHILIAC HCV PLAN 2000 - 2013

Type of Payment	1999 Amount	Paid 2000-2010	Paid 2011	Paid 2012	Paid 2013	TOTAL Paid 2011-2013	TOTAL Paid 2000-2013
4.01(1)(a) Level 1 Fixed Payment	$10,000	$10,817,576.87	$50,976.96	$13,106.48	$13,336.99	$77,420.43	$10,894,997.30
4.01(1)(b) Level 2 Fixed Payment[1]	$15,000 /$20,000	$14,761,073.21	$50,976.94	$26,212.95	$26,673.98	$103,863.87	$14,864,937.08
4.01(1)(b) Level 2 Holdback[2]	$5,000	$4,200,786.80	Nil	Nil	Nil	Nil	$4,200,786.80
4.01(1)(c) Level 3 Fixed Payment	$30,000	$21,064,307.16	$191,163.55	$117,958.29	$160,043.92	$469,165.76	$21,533,472.92
4.01(1)(d) Level 5 Fixed Payment	$65,000	$17,257,324.94	$745,537.86	$340,768.40	$433,452.25	$1,519,758.51	$18,777,083.45
4.01(1)(e) Level 6 Fixed Payment	$100,000	$14,731,971.37	$892,096.59	$786,388.56	$533,479.68	$2,211,964.83	$16,943,936.20
4.02 Loss of Income[3]	N/A	$30,692,216.18	$3,263,961.91	$3,390,686.28	$3,637,546.05	$10,292,194.24	$40,984,410.42
4.03(2) Loss of Services[4]	$12/ hour to $240/week	$24,581,712.18	$2,175,562.99	$1,753,208.17	$1,921,041.64	$5,849,812.80	$30,431,524.98
4.04(a) Cost of Care	$50,000	$2,882,269.17	$593,140.27	$705,490.52	$732,463.08	$2,031,093.87	$4,913,363.04
4.05 HCV Drug Therapy per month	$1,000	$4,684,380.14	$175,869.96	$162,520.60	$385,439.30	$723,829.86	$5,408,210.00
4.06 Uninsured Treatment and Medication	N/A	$2,255,818.43	$206,236.31	$290,825.48	$294,289.09	$791,350.88	$3,047,169.31
4.07 Out of Pockets	N/A	$2,657,634.00	$203,264.81	$164,206.47	$184,049.47	$551,520.75	$3,209,154.75
4.08(2) Alive HIV Co-Infected Option[5]	$50,000	$2,085,299.18	$63,721.19	Nil	$133,369.92	$197,091.11	$2,282,390.29
5.01(1) DB9 Funeral	$5,000	$509,878.37	Nil	Nil	Nil	Nil	$509,878.37
5.01(1) DB9 Estate	$50,000	$4,584,482.63	Nil	Nil	Nil	Nil	$4,584,482.63
5.01(2) DB9 Option	$120,000	$10,383,551.41[6]	Nil	Nil	Nil	Nil	$10,383,551.41
5.01(4) DB9 HIV Co-infected option	$72,000	$10,329,680.60[7]	$91,758.49	Nil	Nil	$91,758.49	$10,421,439.09
5.02(1) DA9 Funeral	$5,000	$439,987.03	$18,614.33	$36,845.91	$34,388.61	$89,848.85	$529,835.88
6.01(1) Loss of Support[8]	N/A	$14,794,972.22	$2,091,581.76	$1,367,877.13	$1,318,738.84	$4,778,197.73	$19,573,169.95
6.01(2) Loss of Services[8]	$12/hour to $240/week	$14,679,525.76	$1,601,188.11	$1,325,358.91	$1,426,296.03	$4,352,843.05	$19,032,368.81
6.02(a) DB9 - FM- Spouse	$25,000	2,273,680.68	Nil	Nil	$33,342.48	$33,342.48	$2,307,023.16
6.02(b) DB9 - FM-Child < 21	$15,000	$1,592,830.74	Nil	Nil	Nil	Nil	$1,592,830.74
6.02(c), (d), (e) DB9 - FM-Child >21, Sibling, Parent	$5,000	$1,881,333.01	Nil	Nil	Nil	Nil	$1,881,333.01
6.02(f), (g) DB9 - FM – Grandparent or Grandchild	$500	$22,849.58	Nil	Nil	Nil	Nil	$22,849.58
6.02(a) DA9 – FM – Spouse	$25,000	$1,946,446.18	$127,442.36	$131,064.76	$166,712.40[9]	$425,219.52[9]	$2,371,665.70
6.02(b) DA9 – FM – Child < 21	$15,000	$657,001.98	$19,116.36	$78,638.84	$80,021.96	$177,777.16	$834,779.14
6.02(c),(d),(e) DA9 – FM – Child >21, Sibling, Parent	$5,000	$2,466,007.67	$203,907.84	$301,449.04	$206,723.50	$712,080.38	$3,178,088.05
6.02(f),(g) DA9 – FM Grandparent or Grandchild	$500	$67,494.73	$13,381.41	$19,659.60	$5,334.80	$38,375.81	$105,870.54
Total Paid		**$219,302,092.22**	**$12,779,500.00**	**$11,012,266.39**	**$11,726,743.99**	**$35,518,510.38**	**$254,820,602.60**

Subtotal Reconciliation **$254,820,602.60**
Less **1,157,116.99** **(Adjustments and credits for other provincial HCV programs)**
Total Reconciliation **$253,663,485.61**[10]

---

[1] Level 2 Fixed Payments were $15,000 until approximately September 2002 when the Courts ordered the Holdback removed and the Fixed Payment increased to $20,000.
[2] The Level 2 Holdback (plus interest) was paid to those persons who had received a Level 2 Fixed Payment while the Holdback was in place.
[3] Loss of Income payments under this provision are for alive HCV Infected Persons and the Estates of HCV Infected Persons who died after January 1, 1999 ("DA9s") where a loss of income incurred prior to death had not already been paid to the HCV Infected Person. Loss of Income payments have been made covering income losses to December 31, 2012. The 2013 payments will be calculated when the claimants provide their 2013 income tax information to the Administrator. Because Dependants of DB9s are entitled to claim Loss of Support provided the death was caused by HCV and because the Loss of Income/Loss of Support software computes a Loss of Income for the actual year of death and thereafter converts the claim to a Loss of Support claim, these payments include Loss of Income payments to Estates of DB9s for the year of death in the amount of $171,664.01 including holdback where appropriate (Claim Nos. 30, 423, 3567, 3677, 5243, 5789, 12180, 1100471, 1100589 and 1100756).
[4] Loss of Services payments under this provision are for alive HCV Infected Persons and the Estates of DA9s where a loss of services was incurred prior to death. Loss of Services payments have been made to December 31, 2012. The 2013 payments are currently being assessed. These payments also include Loss of Services payments in the amount of $312,580.26 mistakenly made to the Estates of DB9s in the years 2001 and 2002 (Claim Nos. 53, 1456, 3920, 4618, 1100139, 1100183, 1100447, 1402726). The Fund was repaid for these payments made in error.
[5] Some HCV Infected Persons did not wish to make an HIV Co-infected election right away. Claimants approved at Level 1 or 2 were paid the Fixed Payment amounts for those levels while they considered the HIV Co-Infected election. If a claimant later made this election, the claimant was paid the difference between the Fixed Payments already received and the $50,000 (indexed) payment available under the HIV Co-Infected Option.
[6] These payments include $229,132.84 coded as Estate payments but paid to Family Members (Claim Nos. 1100345, 1100543, 1100664, 1400511).
[7] These payments include $339,940.94 coded as Estate payments but paid to Family Members (Claim Nos. 432, 2123, 2164, 2252, 2813, 1100378, 1100438, 1100528, 1100757).
[8] Loss of Support/Services payments under these provisions are for Dependants who have suffered a Loss of Support/Services following the death of an HCV Infected Person (either DB9 or DA9) provided the death was caused by HCV. Payments have been made to December 31, 2012. The 2013 payments are currently being assessed.
[9] These payments include $33,342.48 paid to a Spouse in 2013 although not properly coded (Claim No. 20711).
[10] This payment reconciliation equals the adjusted totals calculated from the Access and the Excel databases provided by the Administrator as at December 31, 2013.

C A N A D A
PROVINCE OF QUEBEC
DISTRICT OF MONTRÉAL
NO : 500-06-000016-960

S U P E R I O R C O U R T
Class Action

DOMINIQUE HONHON

Plaintiff

-vs-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Defendants

-and-

ME MICHEL SAVONITTO, ès qualités de membre du Comité conjoint

Petitioner

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A
PROVINCE OF QUEBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000068-987

S U P E R I O R C O U R T
Class action

DAVID PAGE

Plaintiff

-vs-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Defendants

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

AFFIDAVIT

I, RICHARD BORDER, of 980-475 West Georgia Street, Vancouver, BC SWEAR (OR AFFIRM) THAT:

1. I am a Principal and Shareholder of Eckler Ltd. ("Eckler").

2. Attached hereto and marked as **Exhibit "A"** is a true copy of the Eckler Actuarial Report to the Joint Committee Assessing the Financial Sufficiency of the 1986-1990 Hepatitis C Trust as at December 31, 2013.

3. The Eckler actuarial personnel involved in the review of the data and the development of the actuarial model which provides a basis for the opinions expressed are myself, Wendy Harrison, Dong Chen and Kevin Chen. The opinions are those of Wendy Harrison and me and we are the authors of the report.

4. Attached as **Exhibits "B"**, **"C"**, **"D"** and **"E"** are the curriculum vitae of myself, Wendy Harrison, Dong Chen and Kevin Chen.

SWORN (OR AFFIRMED) BEFORE ME)
at Vancouver, British Columbia, on)
11/Mar/2015.)
)
)
)
)
A Commissioner for taking)
Affidavits for British Columbia)

RICHARD BORDER

SHARON D. MATTHEWS, QC
BARRISTER & SOLICITOR
856 Homer Street, 4th Floor
Vancouver, BC V6B 2W5
Tel: 604-689-7555 Fax: 604-689-7554

This is Exhibit "A" referred to in the affidavit of RICHARD BORDER sworn before me at VANCOUVER, BC this 11th day of MARCH 2015

A Commissioner for taking Affidavits for British Columbia

Actuarial Report to the

Joint Committee Assessing the Financial Sufficiency of the 1986-1990 Hepatitis C Trust

as at December 31, 2013

Prepared by:

Richard Border, FIA, FCIA

Wendy Harrison, FSA, FCIA

Vancouver, B. C.

March 11, 2015

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1 Introduction

1. A number of class actions against the Federal and Provincial/Territorial governments were initiated at various dates in 1996 and 1998 on behalf of persons infected with the Hepatitis C Virus ("HCV") from the Canadian blood system during the period January 1, 1986 through July 1, 1990. A Settlement Agreement was subsequently reached as of June 15, 1999.

2. The Settlement Agreement (subsequently approved by the Courts) provided for the creation of a Trust and a Trust Fund from which benefits will be paid. Among other things, the Settlement Agreement set out the amounts of and manner in which funds would be paid by the Federal and Provincial/Territorial governments, investment guidelines thereon, and detail as to those eligible for the various benefits and the amounts of those benefits. The benefits differ according to whether the claimant is a hemophiliac or a non-hemophiliac transfused patient.

3. Section 10.01(1)(i) of the Settlement Agreement requires a triennial assessment of financial sufficiency. In order to do so, we consider the invested assets within the Trust Fund and the notional assets of the Trusts as well as the liabilities of the Trust. We have previously carried out such assessments as at September 30, 1999, December 31, 2001, December 31, 2004, December 31, 2007 and December 31, 2010. The Joint Committee has asked us to complete an actuarial assessment of the assets and liabilities as at December 31, 2013, and we are pleased to report thereon.

4. The intended users of this report are the Joint Committee, Health Canada, the Department of Justice of the Government of Canada, the Provincial and Territorial Governments, and the courts having jurisdiction over the Trust. This report is not intended for or necessarily suitable for users other than the intended users.

2 Approach to the Valuation

5. As has been our approach for all our previous valuations, we have assessed the sufficiency on a going-concern basis. In other words we have assumed that the Trust will continue in operation according to the terms of the Agreements.

6. For this report we have applied a seriatim approach, whereby the liability for the known population is calculated separately for each individual based on their particular circumstances.[1,2]

7. The seriatim model is based directly on the medical model developed by the Medical Model Working Group (the "MMWG", described in more detail in section 6.1) and the software platform used by the MMWG.

8. The objective of this valuation is to establish the financial sufficiency, or soundness of the settlement in light of the available funds. The Canadian Institute of Actuaries'[3] Standards of Practice[4] require that a "provision for adverse deviation" be included when carrying out a calculation that promotes the financial security of an arrangement. Such a provision is incorporated into the liability by using assumptions that are more conservative than "best estimate" assumptions, i.e. by including a "margin for adverse deviation" in the assumption. We explain these terms further in the following paragraphs.

9. A "best estimate" assumption or liability calculation means, in actuarial terms, that it is "*without bias, neither conservative nor unconservative*". In other words, there is a 50% probability that the liability is too high and a 50% probability that it is too low.

10. A "provision for adverse deviation" may be added to the best estimate liability in order to increase the probability that the liability is sufficient (under a range of adverse outcomes).

11. The Standards of Practice address uncertainty in the valuation and the resultant need for a provision for adverse deviation as follows: "*If assumptions could be made with complete confidence, if there were no statistical fluctuations, and if data had no defect, then there would be no need for a provision. But assumptions are virtually always uncertain; the exceptions, such as the assumption of the probability of getting a head when tossing a coin, are rarely encountered in practice. Some, especially*

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[1] For all valuations prior to our 2010 report we had calculated the liabilities using what can be described as an aggregate approach. Under this approach, the claimant population was grouped into age strata and an aggregate liability appropriate for that strata was calculated. This method was appropriate in particular in the context of a large unknown cohort, as it is the only way that the unknown liability could be calculated.

[2] It is not possible to assess the liability for the unknown claimants on a seriatim basis, we therefore valued the liability for unknowns on an aggregate basis whereby the unknown liability is proportional to the known liability.

[3] We are governed professionally by the Canadian Institute of Actuaries.

[4] General Standards of Practice – Part 1000 – Section 1700.

those about events long after the calculation date, may be conjectural. Even when an assumption can be made with high confidence, the result may be subject to statistical fluctuation; one may not get 5 heads when tossing a coin 10 times."

12. The "margin for adverse deviation" is the adjustment to the best estimate assumption that results in an increase in the resulting liability; this increase in the liability is the provision for adverse deviations.

13. The Standards of Practice provide further direction with respect to a provision for adverse deviation: "*The amount of that provision should take account of the effect of the uncertainty of the assumptions and data for the calculation on the financial security of those affected by the calculation, not take account of the possibility of catastrophe or other major adverse deviation which is implausible in usual operations, except when the calculation specifically addresses that possibility, and in the case of a provision in respect of uncertainty of assumptions, result from selection of assumptions that are more conservative than best estimate assumptions.*"

14. Accordingly, in setting the assumptions for this sufficiency valuation, we have included margins for adverse deviations where appropriate, but have not attempted to make provision in the sufficiency liability for catastrophic or other major adverse deviations that are not plausible under usual circumstances, as a provision in the liability for 100% security i.e. a 100% probability that the liability is sufficient, would be considered excessive.

15. We have valued the liabilities on two different bases in this report. Liabilities calculated using the best estimate assumptions are referred to as the "Best Estimate Liabilities". Liabilities calculated using best estimate liabilities and margins for adverse deviations are referred to as the "Sufficiency Liabilities" as these are the liabilities that must be considered when assessing the financial sufficiency of the trust.

16. With respect to future payments under the settlement, there is significant uncertainty that is not provided for in the liability calculation. While the volatility of the financial position arising from changes in the cohort is expected to be much smaller than it was prior to June 30, 2010, the fund is still subject to volatility arising from other factors, in particular, to changes in the medical prognosis (including very promising new treatments), and to changes in the expected benefit payments for non-scheduled benefits such as loss of income or loss of services. In addition, the future investment returns are unknown.

17. As the settlement does not provide for any additional financial resources to be paid into the Trust if the current assets prove to be insufficient, there are no additional sources of funds. The risk to the claimants is asymmetrical: if the ultimate experience of the fund is such that there is money left over, each claimant will have received the promised benefit, but if the opposite occurs, some claimants may receive far less than the Settlement Agreement specifies.

18. Given the ongoing uncertainty about future experience of the settlement, it is prudent to conclude that an excess of assets over the liabilities is required to ensure the ongoing financial soundness of the Trust. The question then arises as to how large the required excess should be.

19. We have developed a Hepatitis C specific framework to systematically assess the sources of risk not covered in the sufficiency liability and develop an appropriate "required capital" for the Hepatitis C fund, in order to protect the claimants from future major adverse experience or catastrophe. This "required capital" represents the amount of assets, over and above those needed to meet the liabilities, that is to be used for the protection, and benefit, of claimants.

3 Summary of Sufficiency Results

3.1 Key Sufficiency Results

20. The table below sets out the key results from the 2013 actuarial assessment of financial sufficiency, as well as the claimant cohort and the corresponding information from the 2010 actuarial assessment. Our methodology, assumptions and detailed results are discussed later in this report.

Key Sufficiency Results[1]		
	2013	**2010**
Cohort	**Count**	**Count**
Transfused - Total Known	3,924	3,840
Transfused - Total Unknown	254	384
Transfused Total	**4,178**	**4,224**
Hemophiliac Total Known	1,359	1,351
Hemophiliac Total Unknown	26	44
Hemophiliac Total	**1,385**	**1,395**
Transfused and Hemophiliac	**5,563**	**5,619**
Assets	**($,000's)**	**($,000's)**
Invested Assets	1,028,048	989,775
Provincial/Territorial Notional Assets	162,152	187,487
Total Assets	**1,190,199**	**1,177,262**
Liabilities		**Restated[2]**
Transfused	480,167	662,772
Hemophiliac	265,957	318,039
HIV Program	970	1,100
Expenses	55,552	34,986
Total Sufficiency Liabilities	**802,646**	**1,016,897**
Excess of Assets over Liabilities	387,554	160,365
Required Capital	151,213	159,500
Excess Capital	**236,341**	**865**

[1] In some cases (in this table and throughout the report), amounts may appear not to add up to the total shown. This occurs because amounts have been rounded to thousands or millions for presentation.

[2] The liabilities set out in our actuarial report assessing the financial sufficiency of the Trust as at December 31, 2010, issued July 27, 2011, totalled $925,577,000. This figure was subsequently revised, as per our Actuarial Report to the Joint Committee Responding to the Morneau Shepell Report on the Financial Sufficiency of the 1986-1990 Hepatitis C Trust as at December 31, 2010, issued November 20, 2012, to $1,016,897,000, to reflect the additional liability arising from deaths that occur at levels prior to level 6 determined to be caused by HCV. The assets in excess of liabilities were correspondingly restated from $251,700,000 to $160,365,000.

3.2 Analysis of Change in Excess Assets

21. We have analyzed the change in the excess asset position approximately as follows:

Summary of Change in Excess Assets	$ millions
Restated excess assets as at December 31, 2010	**160**
Interest on revised excess assets	14
Investment Gain	22
Three year experience gain (loss)	14
Cohort Change	17
Medical model change	370
New drug cost	(146)
Medical model 80% efficacy rate	(65)
Assumption changes	27
Change in methodology for fees and expenses	(25)
Excess assets as at December 31, 2013	**388**

22. The sufficiency of the trust is significantly improved since 2010, with the largest changes arising from the medical model change, the cost of new drugs, and implementation of a margin for adverse deviations on the assumed best estimate drug efficacy rate, as discussed below.

23. While the design of the 2013 MMWG model is essentially the same as previous versions, the expected outcomes are significantly different from the prior MMWG models. It is based on historical data, but also takes into account a number of new treatment protocols, as well as certain promising drug therapies that were "fast-tracked" through the Health Canada approval process. These new drug therapies are expected to be provided to a much larger proportion of the claimants than the therapies taken into account in the 2010 model and their efficacy is significantly higher. As a result the HCV prognosis is significantly better than that shown in previous models. A significant proportion of claimants are projected to clear the virus following treatment with these new drugs. The impact of the improved prognosis on the financial outcome is significant and resulted in a reduction of the liability of $370 million.

24. Offsetting this, the cost of the new therapies is very high and the corresponding liability for future treatment is now significant. This increased the sufficiency liability by $146 million.

25. Due to uncertainty as to the eventual true efficacy of the new treatments, we added a margin for adverse deviations to the treatment efficacy assumption by assuming that the eventual efficacy would be 80% of that assumed by the MMWG. This increased the sufficiency liability by $65 million.

3.3 Required Capital

26. In this report we have assessed the amount of capital required to ensure the soundness of the arrangement based on a first principles Hepatitis C specific approach. We calculate that $151.2 million dollars is required in order to protect the claimants from future major adverse experience or catastrophe. This "required capital" should be regarded as assets, in addition to the assets covering the liabilities, that are to be used for the protection, and benefit, of claimants.

27. The excess assets, or excess capital, i.e. the excess remaining after taking into account the "required capital", is $236.3 million.

4 Summary of Settlement

28. The Settlement Agreement set up three compensation plans: the Transfused HCV Plan ("Transfused Plan"), the Hemophiliac HCV Plan ("Hemophiliac Plan"), and the HIV Secondarily Infected Program ("HIV Program"). The following paragraphs set out the various heads of compensation.

4.1 Transfused Plan

29. The compensation amounts are set out in Articles 4, 5 and 6 of the Transfused Plan. Section 7.03 of the Transfused Plan restricted certain payments initially, subject to revision by the Courts. These restrictions have now all been removed (reduced in the case of loss of income) and are discussed in further detail in the relevant sections below.

30. The cross-references to the relevant sections of the Transfused Plan are shown in parentheses for each item.

31. Most of the prescribed compensation amounts are indexed by inflation each year. In general, we have started with the indexed amounts in effect at January 1, 2014. At January 1, 2014, the prescribed increase over the 1999 values is 34.5774%. Thus, for example, the $10,000 payment (1999 dollars) to each infected claimant under Section 4.01(1)(a) of the Transfused Plan, is increased to $13,457.74 where the payment is made in 2014. For ease of reference we continue to refer to the original 1999 amounts below rather than the actual indexed amounts used in the calculation (e.g. $10,000 instead of $13,457.74). The base 1999 amounts and the indexed 2014 values are summarized in Appendix A.

32. In some instances the dollar expenditures are based on current estimates rather than a prescribed amount, e.g. loss of income, costs of care. In these situations, we derived a compensation level by reference to the actual payouts to obtain the amount assumed payable in 2014. This is discussed further in Section 7 Assumptions.

4.2 Heads of Compensation

33. The following lump sum payments are payable:

4.2.1 $10,000 to Each HCV Infected Claimant (4.01(1)(a))

34. The payments to the known/approved claimants have already been made. All unknown HCV infected claimants who were alive at January 1, 1999 are eligible for this payment on approval as a claimant.

4.2.2 $20,000 to Each Claimant with Positive PCR Test (4.01(1)(b))

35. The $20,000 was originally restricted to $15,000 payable immediately, with $5,000 deferred until there was a favourable reassessment of the fund's assets and liabilities. Following the 2001 review, the Courts lifted the restriction in July 2002 and the full $20,000 is now taken into account. We understand that all the claimants who were originally paid $15,000 have had the additional $5,000 plus interest paid to them, and there is therefore no further liability in this regard.

4.2.3 $30,000 to Each Claimant with Non-bridging Fibrosis (4.01(1)(c))

36. The payments here are to those who have developed non-bridging fibrosis or who have satisfied certain conditions regarding HCV drug therapy.

37. A claimant is allowed to waive the $30,000 payment under this section and in lieu thereof elect compensation for loss of income (Transfused Plan section 4.02) or loss of services in the home (Transfused Plan section 4.03), provided the claimant is at least 80% disabled.

4.2.4 $65,000 to Each Claimant with Cirrhosis (4.01(1)(d))

38. A $65,000 lump sum is payable to all claimants who are at or who enter the cirrhosis stage.

4.2.5 $100,000 to Each Claimant at Decompensation/Cancer (4.01(1)(e))

39. The Transfused Plan includes some other conditions in addition to liver decompensation or cancer. We have assumed that these are all included within the decompensation/cancer probabilities derived by MMWG.

4.2.6 Bridging Fibrosis (4.01(2))

40. Claimants who have developed bridging fibrosis are to be paid the amounts under 4.2.1 $10,000 to Each HCV Infected Claimant (4.01(1)(a)), 4.2.2 $20,000 to Each Claimant with Positive PCR Test (4.01(1)(b)) and 4.2.3 $30,000 to Each Claimant with Non-bridging Fibrosis (4.01(1)(c)) above. The stages of fibrosis development and compensation levels in the Settlement do not directly correspond. As in our previous reports, we have assumed that bridging fibrosis is analogous to stage 3 fibrosis in the model.

41. A number of ongoing payments are made to claimants as follows:

4.2.7 Loss of Income/Services in lieu of $30,000 Lump Sum under 4.2.3 above (4.01(3), 4.02(1)(a) and 4.03(1)(a))

42. As noted in 4.2.3 above, claimants at stage 1 or 2 (i.e. non-bridging) fibrosis may elect to receive loss of income/services in lieu of the $30,000 lump sum.

4.2.8 Loss of Income (4.02(1)(b))

43. In addition to the loss of income already discussed in 4.2.7, compensation is provided for loss of income to those who have developed bridging fibrosis (assumed equal to stage 3 fibrosis in the model), cirrhosis or liver decompensation/cancer.

44. Loss of Income compensation is intended to cover the claimant's net after-tax loss, taking into consideration Canada Pension Plan, Quebec Pension Plan, Unemployment Insurance and/or Employment Insurance premiums and benefits, and certain other collateral benefits.

45. The Transfused Plan initially imposed a $75,000 limit (in 1999 dollars) on the pre-claim gross income used in calculating a claimant's loss of income; this limit was increased by the Courts to $300,000 (in 1999 dollars) effective October 2004. In 2008, the limit was raised to $2.3 million, subject to approval by a court for claims where the pre-loss income exceeds $300,000. Since then four claimants (one with a loss of income of $2.3 million) have been approved. Of the four claimants approved by the courts, one died in 2010, one is now over 65 years old and thus not eligible for any further income loss payments, the third had a net income loss in 2012 of $1,497,000, and the fourth has a net income loss of less than $300,000 (this member had a pre-loss income in excess of $300,000, but has sufficient post-loss income that the income loss paid by the trust is less than $300,000).

4.2.9 Loss of Services in the Home (4.03(1)(b))

46. Compensation for loss of services is available under the same conditions set out in 4.2.8 for loss of income.

47. The compensation payable under this head is set at $12 per hour to a maximum of $240 per week (4.03(2) of the Transfused Plan). This maximum works out to $240 x 52 weeks per year = $12,480 per year (in 1999 dollars).

4.2.10 Costs of Care (4.04)

48. Compensation is available to those who have liver decompensation or cancer, to the extent such costs (other than loss of service in the home) are not recoverable under any public or private health care plan, to a maximum of $50,000 per year.

4.2.11 HCV Drug Therapy (4.05)

49. This compensation (at $1,000 per month - 1999 dollars) is available to those undergoing a regimen of drug treatment that includes ribavirin or interferon.

4.2.12 Uninsured Treatment and Medication (4.06)

50. These costs include claims related to treatments to clear the virus, as well as, for those who do not clear the virus, costs arising from any ongoing treatment related to managing their illness.

4.2.13 Out-of-Pocket Expenses (4.07)

51. Out-of-pocket expenses are expenses other than the uninsured medication costs and costs of care discussed above, and include travel costs to receive medical care and costs of obtaining medical evidence for the purposes of obtaining compensation under the Transfused Plan.

4.2.14 HIV Secondarily Infected (4.08)

52. The Transfused Plan pays compensation above $240,000 in provable claims to those persons who are also receiving compensation under the HIV Program (see Section 4.4 HIV Secondarily Infected).

4.2.15 Deaths Before January 1, 1999 (5.01)

53. The estates of HCV related deaths before January 1, 1999 may elect either $120,000 in full settlement of all claims, including uninsured funeral expenses and loss of guidance, care and companionship ($120K option), or $50,000 plus claims by the family, including uninsured funeral expenses, and loss of support or loss of services ($50K+ option).

4.2.16 Deaths after January 1, 1999

54. Funeral expenses are payable up to a maximum of $5,000 (5.02).

55. **Death Claims after January 1, 1999 - Loss of Support/Services (6.01)**. Both loss of support and loss of services are payable during the remainder of the deceased's life expectancy, as if the death had not occurred, with loss of support converting to loss of services after age 65.

56. **Death Claims after January 1, 1999 - Loss of Guidance, Care and Companionship (6.02)**. The lump sum amounts payable vary between $500 for each grandparent or grandchild, $5,000 for each parent, sibling, or child aged 21 or over, $15,000 for each child under age 21, and $25,000 for a spouse.

4.2.17 Secondarily Infected Persons (3.02)

57. These include spouses of the cohort members, infected via sexual transmission, and perinatal (from mother to fetus) transmission of HCV. The payments to secondarily infected persons are the same as those to primarily infected persons and are as set out above.

4.3 Hemophiliac Plan

58. The Hemophiliac Plan provides for compensation amounts and conditions that are similar in structure to the Transfused Plan, with the following exceptions:

- a claimant who is also infected with HIV may elect to be paid $50,000 in full satisfaction of all other claims including post death claims of dependents and family members (4.08(2) of the Hemophiliac Plan);
- the estates of HIV co-infected persons who died before January 1, 1999 may elect to be paid $72,000 in full satisfaction of all other claims (5.01(4) of the Hemophiliac Plan), even if HCV is not the cause of death.

4.4 HIV Secondarily Infected Program

59. The fund will pay all claims made under the HIV Program at $240,000 per claim to a maximum of 240 claims, as well as costs of administering that program to a maximum of $2 million. No interest is paid on these claims and they are not indexed for the cost of living. In addition, the Transfused Plan and the Hemophiliac Plan both allow for payments in excess of $240,000 in provable claims to those persons who are also receiving compensation under the HIV Program.

4.5 Fees and Expenses

60. Fees and expenses incurred in administering the fund are payable from the fund on judicial approval.

5 Assets at December 31, 2013

61. The costs of the settlement are shared by the Federal and Provincial/Territorial governments in the ratio 8/11 : 3/11. The Federal Government transferred assets in full settlement of its ongoing obligations, while the Provincial/Territorial governments pay their share (3/11ths) of the costs as they arise, subject to a maximum possible payout. Accordingly there are two funds:

- an invested fund containing the remaining balance of the Federal Government funds; and
- a notional Provincial fund that represents the Provincial/Territorial governments' share of the cost of the agreement; this is increased by interest at the rates on three-month treasury bills, less the Provincial/Territorial governments' share of costs to date.

62. The invested assets are invested in two different portfolios: a long term portfolio, divided further into a real return bond portfolio and a portfolio made up of equities and universe bonds, and a short term portfolio invested in short term bonds.

5.1 Asset Development to December 31, 2013

63. The asset development to December 31, 2010 was set out in our previous valuation report.

64. The development of the assets from January 1, 2011 to December 31, 2013 is summarized below. The invested assets and disbursements are taken from the Royal Trust financial statements. The Provinces and Territories' share is taken from the Royal Trust quarterly calculations of interest credits (which are reviewed by us on an ongoing basis). While the Provinces and Territories generally pay their share of the costs as they arise, some have chosen at various times to prepay in anticipation of future costs. At December 31, 2010, both Yukon and Alberta had prepaid balances to their credit which were included in the invested assets. By June 2011, Alberta's prepaid balance had been used up. As a result of further prepayments, at December 31, 2013 Yukon still had a small prepaid balance, while no other Province or Territory had a prepaid balance at the valuation date.

Asset Development from January 1, 2011 to December 31, 2013 ($,000's)			
	Invested Assets	**Notional Assets**	**Total Assets**
Initial, at January 1, 2011	**989,775**	**187,487**	**1,177,262**
Alberta/Yukon unused prepayments = credit balance	(391)	391	-
Investment income/interest credits	120,177	4,837	125,014
Interest credits allocated on prepayments	(1)		(1)
Benefit payments	(75,045)	(28,121)	(103,166)
Fees/expenses	(6,481)	(2,429)	(8,910)
Sub-total	1,028,034	162,165	1,190,199
Yukon unused prepayments = credit balance	14	(14)	-
Closing, at December 31, 2013	**1,028,048**	**162,152**	**1,190,199**

5.2 Composition of Assets

65. The composition of the total invested and notional assets is summarized below:

Asset Distribution at December 31, 2013			
	($,000's)	**% of sub-total**	**% of total**
Long Term Fund			
Real return bonds	697,549	74.5	58.6
Universe bonds	56,253	6.0	4.7
Canadian equity	82,677	8.8	6.9
US equity	49,555	5.3	4.2
International equity	49,420	5.3	4.2
Cash & short-term	475	0.1	0.0
Sub-total	935,929	100.0	78.6
Short Term Fund	92,119		7.7
Total invested assets	1,028,048		86.4
Provinces and Territories' notional assets	162,152		13.6
Total assets	**1,190,199**		**100.0**

66. The investment strategy is passive. In general, the assets in the Long Term Fund are held and not traded. The invested assets, other than the real return bonds that are held directly, are in a variety of index funds managed by TD Asset Management. We understand that the Short Term Fund is drawn down to meet current claims and expenses; it is then reimbursed for the 3/11 share due from the Provinces. We further understand that, from time to time, a portion of the Long Term Fund is re-allocated to the Short Term Fund to rebalance the overall portfolio. The Provinces' notional assets (less their 3/11 share of disbursements) are credited with interest at 3-month treasury bill rates as per the terms of the Settlement Agreement.

5.3 Duration of Fixed Income Assets

67. The duration of the fixed income assets as at December 31, 2010 and 2013 are set out below:

Duration of Fixed Income Assets		
	December 31, 2010[1]	**December 31, 2013**
Real return bonds	11.6 years	15.4 years
Universe bonds	6.0 years	6.7 years
Short term fund	2.6 years	2.8 years

68. Note that the duration[2] of the fixed income assets has lengthened since 2010, in particular for the real return bonds .Lengthening the asset duration was a deliberate strategy to better match the duration of the liabilities[3] as measured in the 2010 assessment. The restructuring commenced in the fourth quarter of 2013 and was completed in early 2014.

5.4 Investment Returns to December 31, 2013

69. The investment returns earned during calendar years 2011 to 2013 were:

Investment Returns By Calendar Year			
Calendar Year	**On Invested Assets**	**On Notional Assets**	**Combined**
2011	11.38%	0.92%	9.76%
2012	3.82%	0.90%	3.42%
2013	(2.84%)	0.98%	(2.31%)

[1] Approximate.

[2] Duration is the weighted average term of the cash flows associated with an asset or a liability and a measure of its sensitivity to changes in interest rates – the longer the duration the greater the sensitivity.

[3] When the duration of the liabilities and assets of an arrangement are equal, the effect of interest rate (real return bond yields in this case) fluctuations is broadly the same on both the assets and the liabilities, hence protecting the arrangement from investment volatility arising from interest rate changes.

70. The 3-month treasury bill rates are summarized below for each calendar quarter between January 1, 2011 and December 31, 2013. These rates were applied to the Provinces and Territories' notional assets in calculating the returns in the table above.

Quarterly 3-month Treasury Bill Rates			
	2011	**2012**	**2013**
Q1	0.98%	0.82%	0.92%
Q2	0.95%	0.93%	0.98%
Q3	0.93%	0.87%	1.03%
Q4	0.81%	0.97%	0.97%

5.5 Excess Investment Returns (Shortfall) to December 31, 2013

71. The 2010 actuarial valuation reflected the assumption that the assets (invested and notional) would earn a real rate of return (i.e. in excess of inflation) of 1.05% per year net of investment-related expenses.

72. The actual inflation increases applied to the Plans' 2010 scale of benefits were 2.84%, 1.76% and 0.91% at January 1, of 2012, 2013 and 2014 respectively.

73. If we bring forward the $1,177,262,000 asset value used at December 31, 2010, adjusted for the actual disbursements (excluding investment-related expenses), to December 31, 2013, with the assumed rates of return, we would expect a total asset value of $1,168,138,000. This compares to the actual asset value of $1,190,199,000. Thus, there was a gain of $22,061,000 (the difference between the actual and expected asset values) on the actual investment returns to December 31, 2013 compared to the long-term actuarial assumption.

5.6 Other Adjustments

74. As at December 31, 2013, there were a number of payments accrued in respect of the known (i.e. approved) claimants at that date; in addition, loss of income and loss of services payments in respect of 2013 are not payable until 2014. These total approximately $11.9 million (combined for the Transfused and Hemophiliac Plans). Provisions for these payments are included with the liabilities set out later in this report.

6 Medical Model and Related Actuarial Model

6.1 Medical Model

75. In 1998, the parties to the Settlement Agreement asked the Canadian Association for the Study of the Liver ("CASL") to construct a natural history model of hepatitis C to aid in the calculation of the various amounts of compensation to patients infected with the hepatitis C virus through blood transfusion between 1986 and 1990. The CASL study was led by Dr. Murray Krahn and was completed in April 1999; its results formed the basis of our assumptions regarding the development of the various medical outcomes for our 1999 actuarial valuation.

76. For each of the 2001, 2004, 2007, and 2010 assessments, a working group convened by Dr. Krahn was retained to review and update the medical model, taking into account the clinical and demographic data from compensation claimants to date. Each of these successive medical models incorporated refinements based on emerging information, while keeping the structure and methodology largely consistent over time. We used these models as the basis for our previous assessments.

77. For the purposes of the current assessment, Dr. Krahn was again retained to convene a working group (the "Medical Model Working Group" or "MMWG") to review the medical model and update it for the additional experience since 2010. We refer to this revised study as the "2013 MMWG"[1] report/study/model.

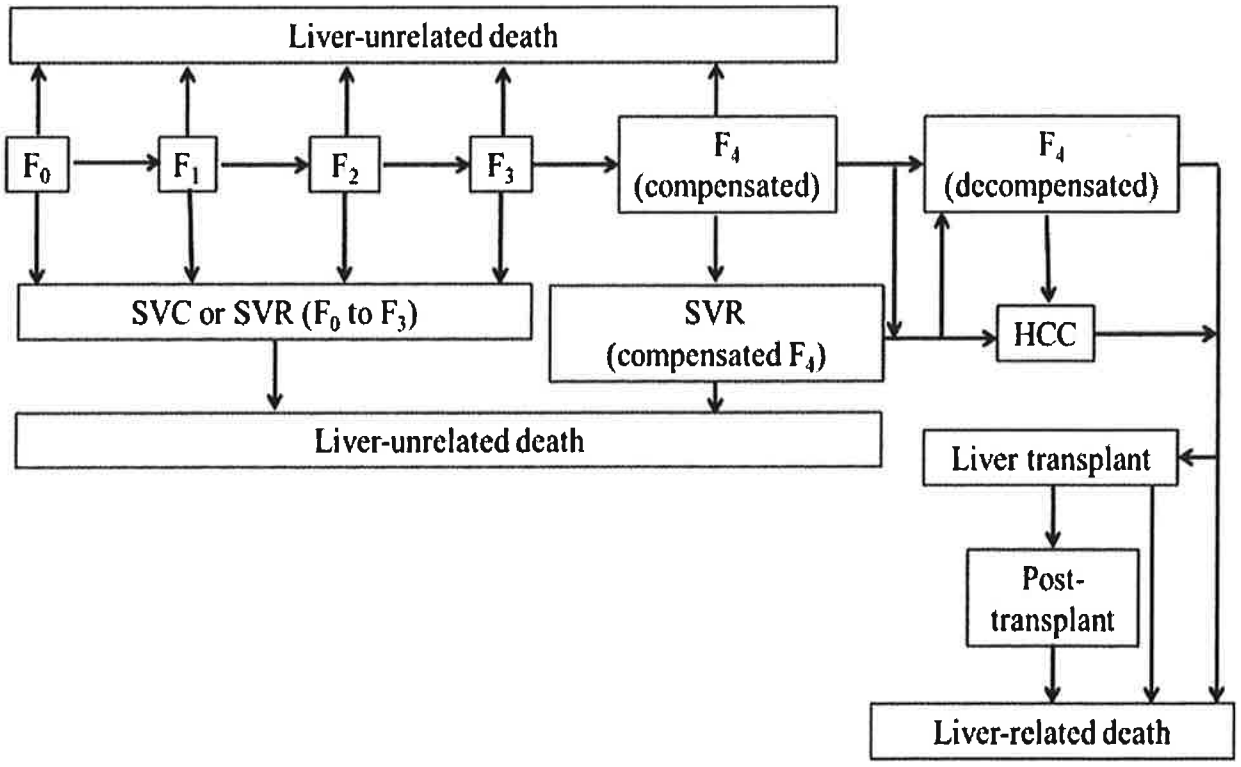
78. The MMWG model is a Markov state transition model. In this type of model, a set of relevant health states or stages is defined; these are shown in the table below. For each projection year, the model applies the appropriate probability of progressing to the next stage.

79. The table below sets out the medical model stages and associated compensation plan levels.

[1] In our previous reports, we referred to the MMWG report, study or model according to the year in which the medical report was issued. For example, the MMWG report used for the 2010 assessment was issued in 2011, so we referred to it as the 2011 MMWG report. Starting with the 2013 assessment, we have changed the naming convention to use the sufficiency review date i.e. 2013 MMWG" instead of "2014 MMWG".

MMWG Stage	MMWG Stage Description	Compensation Plan Levels	Compensation Plan Description
F0 (RNA-)	Fibrosis Stage 0 – RNA negative	1	Claimants who have cleared the virus
F0 (RNA+)	Fibrosis Stage 0 – RNA positive	2	PCR test positive
F1	Fibrosis Stage 1	3	Non---Bridging Fibrosis
F2	Fibrosis Stage 2	3	Non---Bridging Fibrosis
F3	Fibrosis Stage 3	4	Bridging Fibrosis
F4	Cirrhosis	5	Cirrhosis
HCC	Hepatocellular Cancer	6	Cancer
Decomp	Decompensated cirrhosis	6	Liver decompensation
Transplant	Liver Transplant	6	Liver transplant
Death	Liver related death		Death

80. The medical model structure as described in the 2013 MMWG report is shown below[1].



[1] Sustained Virological Response, or "SVR", is defined for this purpose as an undetectable HCV viral load test 12 weeks after completing a successful course of HCV treatment. Spontaneous Viral Clearance or "SVC" refers to undetectable HCV viral load in serum, in the absence of treatment.

81. While the design of the 2013 MMWG model is essentially the same as previous versions the expected outcomes are significantly different from the prior MMWG models. It is based on historical data, but also takes into account a number of new treatment protocols, as well as certain promising drug therapies that were "fast-tracked" through the Health Canada approval process. These new drug therapies are expected to be provided to a much larger proportion of the claimants than the therapies taken into account in the 2010 model and their efficacy is significantly higher. The medical model makes assumptions regarding the proportion of claimants that will be treated with new drug therapies (each claimant is assumed to receive at most one future treatment), and further assumes that these treatments will be provided in the five years from 2014 to 2018. As a result the HCV prognosis is significantly better than that shown in previous models. A significant proportion of claimants are projected to clear the virus following treatment with these new drugs. The impact of the improved prognosis on the financial outcome is significant. Offsetting this, the cost of these therapies is very high and the corresponding liability for future treatment is now significant.

82. The 2013 MMWG model uses a starting age, sex and clinical distribution of the cohort that is based on the observed claimant data, anchored at about August 2013. The MMWG adjusted the observed claimant data to allow for an expected lag in recognition of the actual disease stage of claimants.

83. The MMWG model recognizes the prevalence of HIV infection and hemophilia. While the year-by-year medical transition probabilities do not vary by age, sex or hemophilia in the MMWG model, they are assumed to vary by HIV presence; this, combined with the different age/sex/clinical-stage starting compositions and excess mortality associated with HIV infection, affects the hemophiliac prognosis and leads to different projected outcomes for the hemophiliac cohort compared to the transfused cohort.

84. The MMWG provided the estimated mean and 95% confidence intervals[1] for each of the transition parameters in their report. The 2013 medical model can use either the mean of the distribution in a deterministic[2] projection or the parameter distributions to model a given transition parameter stochastically.

6.2 Actuarial Model

85. For the 2010 valuation we moved to a seriatim approach for valuing the known population, whereby the liability for each claimant is individually calculated taking into account the claimant's specific

[1] The 95% confidence interval indicates that the MMWG is 95% confident (statistically) that the true value falls in the range.

[2] In deterministic models, the output of the model is fully defined or determined by the parameter values and the initial conditions. There is no randomness built into the model, and for a given set of inputs, the same outputs will always be produced.

details (e.g. age, sex, disease stage, actual loss of income claims, etc.). We have continued with this approach for this valuation.

86. The 2014 Markov model developed by the MMWG was analyzed by them using a software package called Treeage Pro 2014. In addition to being able to simulate the progression of individuals through the various health states, this software has the ability to generate future cash flows depending on health state, as well as discount these cash flows to the valuation date.

87. The MMWG shared with us a copy of their medical model as implemented in the Treeage software. We were able to reproduce the MMWG key results, thereby ensuring that we retained the complete medical model as developed by the MMWG; this reduced very significantly any opportunity for errors or misinterpretation arising between the medical model and the actuarial model.

88. We therefore used Treeage Pro 2014 to calculate the known liabilities using a stochastic[1] technique as follows:

- The starting stage distribution of the cohort for financial sufficiency purposes was reset to the observed claimant data, to ensure the timing of benefit payments is correctly reflected.
- We simulated the health state of each individual claimant in each future year by applying the transition probabilities set by the MMWG in their stochastic model. For each future year we calculated the payments due to the claimants based on their projected health state in that year and then discounted the payment amounts to the valuation date to obtain a present value of the future payments.
- We added up the discounted cash flows over all future years to provide an estimate of the liability for the member if they were to progress through the health states as per that simulation.
- The future health states and the associated cash flows for each known member were stochastically modelled, or simulated, 10,000 times and the average of the 10,000 liability outcomes was calculated for the total known cohort. This then represents the liability for future payments for the known population.

[1] Stochastic models use advanced modelling techniques to generate thousands of possible scenarios or outcomes. There is an element of indeterminacy, or randomness, in the potential outcomes; this indeterminacy is described by probability distributions. The model is run repeatedly (possibly thousands of times) with randomly generated inputs, and these probability distributions affect the pattern and distribution of outcomes. The probability of a certain outcome refers to the proportion of trials (or observed frequency) calculated by the model which resulted in the given outcome.

89. The liability for future payments to the unknown claimants was assumed to be proportional to the liability of the known claimants. This is effectively the same as the approach used in previous sufficiency reviews, where the disease stage distribution for the unknown claimants was assumed to be the same as that of the known claimants.

90. In addition to allowing for future payments, there is a liability for amounts payable to unknown claimants immediately upon approval. This liability is for lump sums as well as losses incurred prior to being approved. We allowed for these approximately by calculating the value of lump sum payments based on the assumed stage distribution of the unknowns and allowing for retroactive payment of recurring payments that fell due before the approval date, for example loss of income payments, out of pocket expenses, etc. Retroactive recurring payments will be proportionally less than the historic recurring payments to known claimants as people with significant losses or expenses have a greater incentive to claim, i.e. already come forward for approval. We have allowed for retroactive recurring payments by including $20,000 per unknown claimant in the liability.

91. We calculated the results assuming all unknowns come forward at the valuation date and that past payments are paid immediately and ongoing payments commence at the valuation date. Clearly there will be a delay in unknowns coming forward, but the financial impact of the delay is very small as the unknowns represent a relatively small proportion of the total claimant group and the discounting associated with the delay is small as the net discount rate is so low (see Section 7.4).

7 Assumptions

7.1 Development of Assumptions

92. A significant number of assumptions are required to calculate the liabilities of the trust. The assumptions with respect to disease progression, treatment rates and treatment efficacy were established by the MMWG and documented in their 2014 report. As review of these assumptions is outside our area of expertise, we have adopted these assumptions without modification for use as best estimates in our actuarial model. With respect to the rates of mortality, we have used different assumptions than the MMWG in certain cases, as described further in section 7.5.

93. With respect to all the other assumptions we have worked in conjunction with Morneau Shepell in establishing appropriate assumptions. In setting the assumptions we have used the cohort data provided by the administrator, guidance from, and discussion with, the Joint Committee, as well as other external sources including hepatologists and the insurance industry where necessary, to form a view as to the likely future outcomes.

94. In all cases, Eckler and Morneau Shepell agreed that the assumptions (set out below and in Appendices C to H) are appropriate.

7.2 Best Estimate Assumptions and Margins for Adverse Deviations

95. As noted earlier, a "margin for adverse deviation" is the adjustment to the best estimate assumption that results in an increase in the resulting liability; this increase in the liability is the provision for adverse deviation.

96. The provision for adverse deviation is intended to provide protection against experience that is somewhat worse than the “best estimate” assumption.

97. Use of the expected, or mean, transition probabilities and other medical model parameters would reflect a "best estimate" approach to the liability. As discussed previously in this report, a "best estimate" liability is associated with a 50% probability that it will turn out to be too low.

98. As discussed earlier, it is appropriate in this sufficiency review to incorporate some margins for adverse deviation.

7.3 Cohort Size and Development

7.3.1 Overview

99. The assumption as to the number of claimants that will eventually come forward is important to the results of our valuation. Various theoretical estimates of the number of claimants have been produced since 1998. In addition, there are now about 15 years of actual claims experience. The actual number of claimants who have come forward to date is significantly less than was predicted by the original theoretical estimates. Accordingly, adjustments have been made to the estimated numbers of claimants over the course of the five reports that we have produced.

7.3.2 2013 Cohort Revision

100. The claims deadline was June 30, 2010. Subsequent to the 2010 review, the Courts approved two late claims protocols (CAP1 and CAP2) that allow persons to make claims after this deadline. In addition, there are a number of claims that were submitted prior to the deadline that have not yet been approved. Thus, in addition to the approved or "known" cohort, there is still an "unknown" group of claimants that have yet to be approved, either because their claim has not yet been approved, or because they have not yet applied for approval. An estimate of these unknowns is required. We have arrived at this estimate by making assumptions as to the number of future CAP1 and CAP2 claims and applying assumed approval rates to these as well as the regular in-process claims.

101. The administrator has provided us with data on 3,924 approved transfused claimants as at December 31, 2013, consisting of 3,740 alive or deaths after January 1, 1999 (DA9s), and 184 who died before January 1, 1999 (DB9s). In addition the Administrator has indicated that there are a further 290 (net of 195 archived claims[1]) as yet unapproved claims in process at December 31, 2013, totaling 254 alive or DA9s, and 36 DB9s.

102. By December 31, 2013, 65 persons had claimed under CAP1 and 9 persons under CAP2. In addition, a further 30 CAP1 and 30 CAP2 claims were made in 2014.

103. The approved CAP1 and CAP 2 claims are summarized below:

[1] Old claims that were submitted for approval, but where the claimant has not continued with the approval process and it is not expected that an approved claim will result.

Number of Approved Claims Under CAP1 and CAP2		
Approval Year	**CAP1**	**CAP2**
2010	1	0
2011	0	1
2012	44	8
2013	20	0

104. Based on the table above, and information from the administrator regarding claims submitted in 2014, we have assumed 98 CAP1 and 77 CAP2 claims after 2013. The approval rate for CAP1 up to and including 2013 was 47% and the corresponding CAP2 approval rate was 78%. We have assumed that the best estimate future approval rates will be 45% and 70% respectively giving a total of CAP 1 and CAP2 unknowns of 98 (=98x45%+77x70%).

105. The approval rate for all claims up to 2013 is as follows:

Year	Submitted	Approved	Denied (including archived claims)	Pending (net of archived claims)	Approval Rate
Primarily Infected					
2000	2,912	2,051	858	3	71%
2001	1,091	655	430	6	60%
2002	609	338	268	3	56%
2003	338	192	144	2	57%
2004	249	127	120	2	51%
2005	210	107	96	7	53%
2006	170	100	62	8	62%
2007	117	52	59	6	47%
2008	102	50	44	8	53%
2009	101	52	44	5	54%
2010	471	110	148	213	43%
2011	4	1	3	0	25%
2012	53	29	22	2	57%
2013	21	6	9	6	40%
Total	**6,448**	**3,870**	**2,307**	**271**	**63%**
Secondarily Infected					
Total	**160**	**54**	**87**	**19**	**38%**

106. As can be seen from the above table, the approval rate has generally fallen over time. Further, we expect that the longer it takes to approve a claim, the less likely it will be that the claim will eventually be approved. As a result we have assumed that the best estimate approval rate for primarily infected claims (other than CAP1 and CAP2 claims after 2013) will be 55% and that secondarily infected claims will be have a best estimate 38% approval rate.

107. Applying these approval rates to the in process claims we obtain 156 regular unknowns, including 20 DB9s.

108. To show the sensitivity of the results to the number of claimants coming forward and to variation in the denial rate for the unapproved claims in process, we have calculated the cost of 10 additional approved transfused claims. This sensitivity is discussed further in Section 11.

109. The Administrator has provided us with data on 1,359 approved hemophiliac claimants as at December 31, 2013, consisting of 1,058 alive or DA9s, and 301 DB9s. In addition there are a further 19 (net of 9 archived claims) as yet unapproved claims in process at December 31, 2013, totaling 15 alive or DA9s, and 4 DB9s; and, applying an approval rate of 85% (the approval rate for hemophiliac claims since 2007, i.e. the approval rate in the more recent past), this results in a further 14 alive or DA9, plus 2 DB9s.

110. In addition, based on the rate at which hemophiliacs have claimed under CAP1 and CAP2 in 2014, we have assumed that 12 hemophiliacs will claim under CAP1 and none under CAP2 and that the approval rate will be 80%. This results in a further 10 hemophiliac unknowns, consisting of 9 alive or DA9s, plus 1 DB9s.

111. Therefore, there are 1,385 hemophiliac persons that will ultimately claim. Of these, 1,081 are alive or DA9s (23 yet to come forward), while 304 are DB9s (3 yet to claim).

112. Included in the hemophiliac totals discussed above are 8 hemophiliac secondarily infected approved claims, and we have assumed that no further secondarily infected hemophiliac claims will be approved. Of the known secondarily infected claimants, all were alive at December 31, 2013.

113. The distribution of the known alive cohort as at December 31, 2013 is shown in Appendix A. Separate tables are shown, first indicating the number of claimants and percentage allocations of the known transfused cohorts by age and clinical stage at December 31, 2013 (Appendices A-1 and A-2); next, the hemophiliac number of claimants and percentage distributions by age and clinical stage, as at December 31, 2013, are included in Appendices A-3 and A-4.

7.3.3 Further Hemophiliac Cohort Assumptions

114. At the valuation date, 62% of the known applicants who were alive at January 1, 1999 are still alive and 38% of the known applicants alive at January 1, 1999 have subsequently died. We have assumed that the 23 alive at January 1, 1999 who are yet to claim will present in the same proportion, i.e.

14 will be alive and 9 will be DA9s and their stage distribution will be the same as the stage distribution of the known claimants.

115. Currently 26% of the known alive and DA9 claimants are HIV co-infected. We have assumed that the same percentage of the unknown claimants will be co-infected and that 100% of the co-infected at level 1 will take the $50K option. This results in three $50K option claims. The rest of the alive and DA9 unknowns will claim under the regular heads of compensation, which are triggered by disease progression and other losses.

7.4 Net Discount Rate

116. The lump sum present value of future benefit and expense payments depends on two main economic parameters. The first is the gross rate of investment return that will be earned or credited on the fund's assets. The second is the rate at which the future payments may be expected to increase (most of the benefits under the plan are scheduled to increase in accordance with increases in the Consumer Price Index).

117. The foregoing two parameters affect the calculation of the lump sum present value in opposite directions. The higher the rate of investment return that is used in discounting the future payments to the present time, the lower will be the resulting lump sum present value; the higher the rate that the payments are assumed to increase in the future, the higher will be that resulting present value.

118. A precise present value calculation would require a formula incorporating the gross rate of return and the rate of inflation as separate parameters. However, virtually the same result will flow from a simpler formula where the future payments are discounted at a net rate equal to the excess of the gross rate of return over the assumed rate of inflation.

119. We developed the net discount rate for this valuation as follows. First, we established expected long term returns for each of the asset classes invested in by the fund (including the Provincial/Territorial notional assets which are effectively invested in treasury bills). Then, taking into account the standard deviation of each asset class's returns (the standard deviation is a measure of how variable returns have been historically and commonly used as an indication of investment risk) and the historical correlations between the asset class returns (the degree to which the asset class returns are related to each other), we modeled the expected return from the overall portfolio based on the target asset mix. This approach allows us to capture the effect of the diversification in the portfolio. We then subtracted an explicit inflation assumption, to derive a "best estimate" of the net rate of return.

120. As discussed in Section 7.2, it is not appropriate to use a best estimate of the net return as the discount rate. We therefore introduced a margin for adverse deviations in investment returns and accordingly reduced the best estimate net discount rate to arrive at the sufficiency valuation assumption.

121. The expected returns and standard deviations[1] assumed for each asset class are shown in the table below:

%	3-Month Treasury Bills	Universe Bonds	Short Term Bonds	Real Return Bonds	Canadian Equity	Global Equity
Expected Return	3.1	4.1	4.1	2.9	7.6	7.7
Standard Deviation	2.0	6.0	3.4	11.4	17.5	17.4

122. The asset allocation is derived by allocating $92 million of the invested assets to the Short Term Fund (as per the current allocation to the Short Term Fund) and the balance of the invested assets as at December 31, 2013 to the Long Term Fund, invested in line with the Long Term Fund benchmark asset allocation, together with the actual Provincial/Territorial Notional Assets as at December 31, 2013:

Fund	Asset Class	Asset Allocation	Fund Allocation	Total Asset Allocation
Long term Fund			**78.7%**	
	Real Return Bonds	80.0%		62.9%
	Universe Bonds	6.0%		4.7%
	Canadian Equity	7.0%		5.5%
	US Equity	3.5%		2.8%
	EAFE Equity	3.5%		2.8%
Short term Fund			**7.7%**	
	Short term bonds	100.0%		7.7%
	Cash	0.0%		0.0%
Provincial/Territorial Notional Assets	**3 Month Treasury Bills**	**100.0%**	**13.6%**	**13.6%**

[1] The mean returns and standard deviations were calculated using historical experience by asset class over a 20 year period.

123. The resulting best estimate and sufficiency valuation net discount rates are:

Component of Return	**%**
Best Estimate Return	3.84
Investment Expenses	(0.04)
Best Estimate Nominal Return	3.80
Best Estimate Nominal Return rounded to nearest 10th%	**3.80**
Best Estimate Inflation	2.50
Best Estimate Net Discount Rate	**1.30**
Margin for Adverse Deviation	0.25
Sufficiency Net Discount Rate	**1.05**

124. The above method also allows us to investigate the statistical distribution of returns and hence calculate, for example, the 95th percentile returns. This is important when assessing the required capital framework as discussed in Section 9.

125. The discount rate used in the 2010 valuation was derived using the same method as that described above. The best estimate net discount rate and the sufficiency valuation net discount rate are unchanged from 2010.

126. The best estimate net discount rate is used when calculating the best estimate liabilities. The sufficiency net discount rate is used in calculating the liabilities with provision for adverse deviations used in assessing the sufficiency of the fund.

127. In order to illustrate the sensitivity of the results to variations in the valuation net discount rate, we have also calculated the liability using a more conservative 0.8% per year (this increases the present value of the liabilities).

128. We have continued to ignore the effect of income tax on the investment returns since the Settlement Agreement provides that if any such taxes are paid they will be reimbursed to the fund.

7.5 Mortality Assumptions

129. In their previous reports, the MMWG used standard Canada life table mortality for non-liver related deaths on the basis that any extra mortality related to the health problems that had required blood transfusions was no longer present due to the passage of time. For their 2014 report, the MMWG analyzed cohort mortality experience and used mortality rates derived from the data for most ten year age bands (see pages 32 - 34 of the MMWG report). The data used to derive these rates is extremely sparse:

19 male hemophiliac deaths, 5 female hemophiliac deaths[1], 124 male transfused deaths and 61 female transfused deaths). In our opinion, this data is insufficient to derive mortality rates that can be considered to be calculated in accordance with accepted actuarial practice and therefore we are unable to use the mortality rates derived by the MMWG in our financial assessment. Instead we assumed non-liver related mortality rates would be as per the Canada Life Tables 2009 – 2011. The effect of this modification of the MMWG assumption is immaterial. The limited evidence from the MMWG analysis suggests that actual mortality for both the hemophiliac and transfused groups could be somewhat higher than the Canada Life tables' mortality, but no allowance was made for future mortality improvements (general population mortality is expected to improve over time), which compensates for this to some degree. Because the results of the assessment are not particularly sensitive to this mortality assumption, no margin for adverse deviation was applied.

130. Life insurance underwriting manuals indicate that hemophiliacs have higher mortality rates than non-hemophiliacs. In previous reports, the MMWG discussed this issue and pointed out that other than increased mortality due to HIV infection and liver disease, the underlying mortality of hemophiliacs was the same as non-hemophiliacs (Page 51 of the 2010 MMWG Report). As the mortality associated with HIV co-infection and end stage liver disease is explicitly allowed for in the medical model, no additional mortality adjustment is required for hemophiliac's mortality and the Canada Life Tables 2009-2011 mortality rates are used for non-liver related mortality for hemophiliacs without HIV co-infection.

131. For HIV co-infected, we have concerns regarding developing mortality rates from the cohort data as was done in the MMWG report (page 36) due to the paucity of data. Accordingly, we have assumed mortality rates at 624% of the Canada Life 2009-2011. The 624% adjustment was calculated by the MMWG in their 2010 report based on a meta-analysis of four studies with significantly more data than available from the cohort (the cohort based rates were based on 11 deaths over a ten year period, which in our opinion is insufficient to develop meaningful mortality rates). Because this assumption affects a relatively small portion of the liability, no margin for adverse deviation has been applied.

132. For mortality associated with liver-related diseases, we based our assumption on the rates derived by the MMWG, with one adjustment. For HIV co-infected claimants, at older ages it is possible for the 624% of the Canada Life Table 2009-2011 mortality rates to exceed the liver-related mortality rates derived by the MMWG. As a result, we have assumed that mortality for HIV co-infected claimants will be the greater of the MMWG derived rate and 624% of the Canada Life Table 2009-2011 rates. The data that the MMWG relied on to derive the liver-related mortality rates is somewhat sparse, but we understand that this mortality is significantly higher than general population mortality, and we have no better source for this assumption.

[1] Hemophilia is a genetic disorder that rarely affects females. However, persons who qualify under the hemophiliac plan have medical conditions broader than hemophilia, hence the presence of female deaths in the hemophiliac data.

133. The medical model makes explicit allowance for HCV liver-related deaths only at stage 6. In practice, some deaths at earlier stages are determined to be HCV related and claimants compensated as such. Based on an analysis of the proportion of deaths being compensated as HCV deaths at each stage we derived appropriate assumptions to reflect this. No margin for adverse deviation was applied to this modified assumption; rather, an allowance for additional HCV related deaths was made in the required capital calculation.

7.6 Treatment to Clear the Virus

134. The medical model assumes there are three[1] categories of treatment drugs that will be offered to claimants: PEG-IFN/RBC-based triple therapy; Sofosbuvir-based doublets; and 3D regimen plus RBV.

135. After the 2013 MMWG report was completed, and while we were developing this report, other drug regimens have been introduced, for example, 3D regimen without RBV. We have not attempted to modify the medical model to reflect these new regimens.

136. The medical model also makes assumptions as to the percentage of claimants who will receive each of these three categories of treatment drugs. These percentages vary depending on whether the claimant was previously treated, and whether the claimant is co-infected with HIV, resulting in four classes of treatment prevalence. We have adopted these assumptions, which are set out in Appendix E.

137. The Joint Committee provided us with medical evidence summarizing the current HCV treatment protocols in Canada, including the 2015 CASL guidelines and medical information from Dr Bain (a hepatologist called on by the Joint Committee to provide guidance on HCV treatment protocols). These protocols specify the typical treatment comprising choice of drug, whether additional drugs are included, and treatment duration. Treatment durations generally vary from 8 weeks to 24 weeks, with 12 weeks being by far the most common. The protocols may vary depending on a number of factors, including whether the individual has been previously treated, the disease stage of the individual (for example, whether the claimant is cirrhotic) and the genotype of the virus.

138. We developed a distribution of treatment drug and duration for known alive claimants, by applying these protocols according to claimant data (which indicated whether previously treated, whether co-infected, and disease stage) and an assumed distribution of genotype for the claimant cohort.

139. From this distribution of treatment drug and duration, we calculated the weighted average treatment duration for each of the three categories of HCV treatment drugs.

[1] Four different treatment categories were initially considered by the MMWG, but the results of a survey of physicians specializing in HCV (upon which the MMWG based their treatment assumptions) indicated that no doctors would prescribe the oldest drug, and it was effectively dropped from the medical model.

140. The Joint Committee provided us with information on costs of these HCV treatment drugs, reflecting input from the administrator and the medical evidence from Dr. Bain, based on a standard treatment duration of 12 weeks. One of the HCV treatment drugs was only approved for use in Canada in December 2014 and as such actual costs are not yet available; we assumed that the cost of this drug would be the same as that of the most recently approved drug for which we have actual costs available.

141. We adjusted these drug costs to reflect the average treatment durations described in paragraph 139; this formed the basis for our best estimate of drug treatment costs assuming 100% of the cost is reimbursed by the HCV Trust: $60,000 for PEG-IFN/RBC-based triple therapy, and $85,000 for each of Sofosbuvir-based doublets and 3D regimen plus RBV.

142. Taking into account the uncertainty associated with the assumptions regarding these very new HCV treatment drugs, uncertainty which could arise from drug costs per treatment or dose higher than expected and/or treatment durations longer than expected, we applied margins for adverse deviations to these best estimate assumptions, resulting in a sufficiency assumption of $110,000 per course of HCV drug treatment for each of the three categories. We believe the margin for adverse deviation with respect to HCV drug treatment cost, which is proportionately larger than the margins applied in most other normal situations, is appropriate in these circumstances.

143. Of the three categories of drug treatments that were assumed in the medical model, one (PEG-IFN/RBC-based triple therapy) is no longer included in the HCV drug treatment protocol in Canada. This drug has a lower average best estimate cost than the other two drugs, but a lower treatment efficacy. It is our understanding, based on the 2015 CASL guidelines and medical evidence from Dr. Bain, that newer drug options would likely be prescribed instead. The proportion of claimants assumed to be treated with this older drug was lower than the other two options. We did not modify the medical model to eliminate this older drug as a treatment option, as assumptions regarding treatment protocols are beyond the scope of our expertise. We believe the impact of retaining this older drug in the model results in liabilities which are slightly higher than they would otherwise have been.

144. The HCV trust pays only that portion of the HCV treatment drugs that is not reimbursed by either a provincial or private health plan.

145. The medical model assumes that all claimants who are eligible for treatment will be treated over a five year period starting in 2014. We assumed that over this period, none of the drug treatments would be eligible for reimbursement from a provincial drug plan (in other words, by the time these drugs are generally covered under provincial health plans, the claimants have already been treated and reimbursed by the HCV Trust).

146. We assumed that, on average, 50% of the claimants under age 65 would be covered under a private health insurance plan, and that the private health insurance plan would reimburse 80% of the costs; this leaves 60% (the balance after 50% of 80%, or 40%, is reimbursed by the private plan) to be paid by the HCV Trust. These assumptions were derived from data from the administrator showing historical rates of private insurer drug coverage for HCV claimants combined with our understanding of private insurance coverage in the Canadian population, and data from private insurers showing average reimbursement rates for newer HCV treatment drugs.

147. Using the same weightings as were used to derive the treatment durations for each of the three categories of HCV treatment drugs (which were based on the medical evidence provided by the Joint Committee), we developed weighted overall average treatment duration of 13.2 weeks; this was used as our best estimate assumption for duration of drug therapy. We applied a margin to this assumption to obtain the sufficiency assumption of 14.5 weeks.

148. The HCV treatment drugs have evolved dramatically and rapidly in recent years. Drug treatments contemplated in medical model have changed dramatically from the 2010 to 2013 medical models, and, as noted in paragraph 143, certain drug treatments taken into account in the 2014 model, developed in 2013 and 2014, are no longer offered. The field is changing quickly, and other new drugs may emerge, either replacing the current drugs, or enabling more effective treatment of individuals who are currently hard to treat.

7.7 Other Assumptions

149. The 2013 valuation required a number of other assumptions, e.g. proportion of claimants claiming loss of income/services/support at various disease levels, their average percentage of disability, income/support levels, costs of care, drug costs, other expenses, death benefits and so on. We, together with Morneau Shepell, derived appropriate assumptions based on analysis of the claims experience to the valuation date, consideration of the assumptions used in previous valuations, as well as expert medical and other advice.

150. These assumptions differ in some instances between the transfused and hemophiliac plans. We show the assumptions in detail in Appendix F.

151. As discussed in Section 7.2, we start with best estimate assumptions, but for the sufficiency valuation we require assumptions which include margins for adverse deviations. We have not taken margins on all assumptions, only those where there is either a large degree of uncertainty as to the eventual outcome and/or where the overall liability is a large component of the total.

152. This section describes the approach and considerations taken into account in setting the assumptions. The assumptions used are set out in detail in Appendix F.

7.7.1 Lump Sum Payments

153. Lump sum payments are made when a claimant reaches specific stages of the disease. For known claimants, allowance is made for future payments based on their projected progression through the disease per the MMWG model. For unknown claimants, all stage related payments based on their assumed disease stage at the time of approval as a claimant are allowed for, together with future payments based on their projected progression through the disease.

7.7.2 Loss of Income and Loss of Services

154. The assumptions regarding loss of income and loss of services claims may vary depending on the claimant's disease stage, whether the claimant is already claiming one of the benefits, and whether the claimant is projected to clear the virus on treatment or not.

155. For claimants already receiving loss of income or loss of service payments, the actual loss at the valuation date is taken into account. In stochastic projections where the claimant does not clear the virus on treatment, the actual loss is assumed to continue until age 65 or earlier death for loss of income, and for life for loss of services.

156. For claimants not yet receiving loss of income benefits, future loss of income or loss of services benefits are assumed to be paid at an annual rate derived from the average loss of income/loss of services amounts currently in pay.

157. We analyzed the proportion of claimants receiving loss of income/loss of services at each disease stage to derive probabilities of claiming at each disease stage. These probabilities are set such that the proportion of claimants who have not yet cleared the virus receiving such payments in the future is the same as the proportion of those who have not yet cleared the virus currently receiving such payments. In other words, as current claimants who have not yet cleared the virus move on, or are projected to die, new claimants are projected to replace them at a rate such that the total percentage of claimants who have not yet cleared the virus receiving payments remains constant.

158. For claimants who are projected to clear the virus before going on loss of income or loss of services we assume that they will not receive loss of income or loss of services payments.

159. For claimants who are projected to clear the virus on treatment, allowance needs to be made for recovery and return to work, or return to household duties. The amount of data on cured claimants who were receiving loss of income or loss of service benefits is quite limited. It did show, however, that a

significant proportion of claimants have continued to receive loss of income/loss of service payments after clearing the virus, especially in cases where the loss has been in payment for a long time.

160. There are no studies that we are aware of that investigate the return to work outcomes for HCV infected people on clearing the virus, so we were unable to identify external data that was directly applicable in this regard. The Joint Committee consulted Dr Bain and Morneau Shepell consulted Dr Wong (a hepatologist) for further insight on likely recovery rates,

161. We considered disability tables developed by actuaries for use in life insurance as a further source of information on disability recovery rates. These tables, and associated studies, do not provide any specifically useful data on recovery rates as the disabilities covered are broader than HCV. They do show, however, that recovery rates decline the longer the claimant has been on disability. This is consistent with the recovery data (limited as it is) of the fund, and so we established recovery rates that are duration dependent. In other words, the longer the person has been receiving loss of income or loss of service payments the less likely that these payments will stop on successfully clearing the virus. The rates assumed are shown in Appendix F.

162. The Loss of Income and Loss of Services benefits comprise a significant portion of the liability, and there is considerable uncertainty about the probability of recovery following a cure as a result of HCV treatment. We therefore applied a margin for adverse deviation to the recovery assumption.

163. We developed assumptions regarding the benefit amounts for future Loss of Income and Loss of Services claims based on the experience of the Trust, taking into account differences between transfused and hemophiliac claimants, and trends in the data.

164. A review of the annual loss of income payments to individuals shows considerable variation in benefit amounts; we therefore applied a margin for adverse deviation to this assumption.

165. The Transfused Plan initially imposed a $75,000 limit (in 1999 dollars) on the pre-claim gross income used in calculating a claimant's loss of income; this limit was increased by the Courts to $300,000 (in 1999 dollars) effective October 2004. In 2008, the limit was raised to $2.3 million, subject to approval by a court for claims where the pre-loss income exceeds $300,000. Since then four claimants (one with a loss of income of $2.3 million) have been approved. Of the four claimants approved by the courts, one died in 2010, one is now over 65 years old and thus not eligible for any further income loss payments, the third had a net income loss in 2012 of $1,497,000, and the fourth has a net income loss of less than $300,000 (this member had a pre-loss income in excess of $300,000, but has sufficient post-loss income that the income loss paid by the trust is less than $300,000).

7.7.3 Cost of Care

166. Analysis of the cohort data shows that average claim amounts are approximately $30,000 and that about 40% of those at Stage 6 will claim for cost of care.

167. A review of the cost of care payments to individuals shows considerable variation in benefit amounts; we therefore applied a margin for adverse deviation to this assumption.

7.7.4 HCV Drug Therapy

168. HCV Drug Therapy payments are made to claimants receiving a drug treatment regimen that includes ribavirin or interferon. Prior to the emergence of the recent HCV treatment drugs, all HCV treatments incorporated one or both of these drugs. While we recognize that the most recent drug regimens, which were approved after development of the medical model, may not include these drugs, we have assumed that Drug Therapy payments will be made to all claimants receiving treatment to clear the virus for the same length of time that we have assumed treatment will take. See section 7.6 for a discussion on assumed treatment length. To provide insight into the effect of overstatement in this assumption as a result of changes in treatment regimens in the future, we have included a sensitivity result showing the impact of reducing the number of claimants for HCV drug therapy payments by 50%.

7.7.5 Uninsured Treatment and Medication

169. For claimants who do not clear the virus, we have allowed for ongoing uninsured treatment and medication. The amount per year was set equal to the average (rounded up to the nearest $500) uninsured treatment and medication costs after removing expenses related to treatment aimed at clearing the virus. Likewise the percentage of claimants receiving such payments is derived from the administrator data. The analysis has been done separately for Transfused and Hemophiliacs.

170. For uninsured costs related to treatment to clear the virus we have used the assumptions discussed in Section 7.6 Treatment to Clear the Virus above.

7.7.6 Out-of-Pocket Expenses

171. Out-of-pocket expenses are expenses other than the uninsured medication costs and costs of care discussed above, and include travel costs to receive medical care and costs of obtaining medical evidence for the purposes of obtaining compensation under the Transfused Plan.

172. For claimants who do not clear the virus, we based our out-of-pocket expense assumption on the experience of the trust. We did not apply a margin for adverse deviation to this assumption, which has remained relatively stable over the last few assessments.

173. For claimants who clear the virus, we expect that the out-of-pocket expenses will reduce significantly, but the cohort data is too sparse to be useful in setting an appropriate assumption. We reviewed "Patient time costs and out-of-pocket costs in hepatitis C", a study of out of pocket expense claims (and other ongoing costs) in BC published in Liver International, 2011, to see if it provided any insights. The study showed that out-of-pocket expenses continue to be incurred after successful treatment, but given the generally short period between successful treatment and the study date, it was not conclusive that out-of-pocket expenses will continue in the long term. Accordingly, we have set an assumption (expressed as a single present value payment, payable on successful treatment) that takes into account our expectation that out-of-pocket expenses will reduce considerably on clearing the virus. Since there is considerable uncertainty surrounding this assumption, we applied a margin for adverse deviation.

7.7.7 Funeral Costs

174. Funeral costs are payable up to $5,000 for both HCV related deaths before January 1, 1999 and HCV related deaths after January 1, 1999. Analysis of the average funeral costs paid by the fund show that average amount paid per death is not at this maximum rate. We have set an assumption based on the average claim amount and assumed that 100% of deaths will result in a funeral claim. We did not apply a margin for adverse deviation to this assumption.

7.7.8 Deaths Before January 1, 1999

175. The estates of HCV related deaths before January 1, 1999 may elect either $120,000 in full settlement of all claims ($120K option), or $50,000 plus claims by the family, including loss of support or loss of services ($50K+ option).

176. We have analyzed the cohort data to obtain the percentage choosing each option, the average payments to the family under the $50K+ option and percentage receiving loss of support and loss of services. Loss of services are assumed to be paid the same rate as loss of services to alive claimants, while the loss of support is assumed to be paid at the average rate in the cohort data.

177. For five claimants who chose the $50K+ option the total payments to date are less than $120,000 we have anticipated that further claims will be forthcoming (i.e. their claim will be worth more than the $120K option) and allowed for an additional liability in this regard.

7.7.9 Deaths After January 1, 1999

178. Both loss of support and loss of services are payable during the remainder of the deceased's life expectancy, as if the death had not occurred, with loss of support converting to loss of services after age 65.

179. For simplicity we have assumed a life expectancy of 85 for both males and females, and allowed for payments from the age at death to this age. Strictly speaking, life expectancy increases the older the attained age, for example the life expectancy of a 60 year old is higher than the life expectancy of a 40 year old, but our simplified approach will result in a liability that is not materially different to the liability that would be calculated using the slightly more accurate attained age life expectancies.

180. Where loss of income or loss of services were being paid prior to death, it is assumed that corresponding claims will be made for loss of support or loss of services after death. The loss of support will be at 70% of the loss of income amount and loss of services will continue at the pre death level.

181. Where loss of income or services were not being paid prior to death we have assumed payments will be made at the average rate in the cohort data and the percentage claiming each type of payment will be as per the cohort data to date.

182. Death Claims after January 1, 1999 - Loss of Guidance, Care and Companionship. The lump sum amounts payable vary between $500 for each grandparent or grandchild, $5,000 for each parent, sibling, or child aged 21 or over, $15,000 for each child under age 21, and $25,000 for a spouse. Care and guidance is assumed to be paid at the average rate in the cohort data.

7.7.10 HIV Secondarily Infected Payments in Excess of HIV Program Payments

183. The Plans pay compensation above $240,000 only in provable claims to those persons who are also receiving compensation under the HIV Program (see Section 4.4). The Joint Committee expects this group to be extraordinarily small or non-existent and therefore, as in previous valuations, we have not performed any calculations pertaining to this limit. There have been no such claims to date.

7.7.11 Secondarily Infected Persons

184. These include spouses of the cohort members, infected via sexual transmission, and perinatal (from mother to fetus) transmission of HCV.

185. We have combined the secondarily infected persons with the primarily infected persons when calculating the liability for each head of compensation, therefore, no liability has been separately identified for those secondarily infected persons.

7.7.12 Outstanding 2013 Payments for Known Claimants

186. As noted in Section 5.6, there were a number of payments relating to calendar 2013 that were outstanding in respect of the known/approved claimants as at December 31, 2013. These total approximately $6,390,000 in respect of the Transfused Plan claimants and $5,521,000 for hemophiliacs.

7.7.13 Delay in Commencement of Payments to Unknown Claimants

187. As noted in Section 6.2, the above liability amounts assume that all unknowns come forward at the valuation date and that all due amounts are paid immediately. In reality there will be a delay before the payments to the unknowns commence, however, given the small size of the unknown cohort and the low discount rate we have not made allowance for this.

7.7.14 Claimants with Cryoglobulinemia and Glomerulonephritis

188. There are 25 claimants at Level 6 who have either Cryoglobulinemia or Glomerulonephritis who were excluded from the MMWG modelled outcomes on the basis that they are good candidates for treatment and that their prognosis would improve significantly on successfully clearing the virus.

189. Based on the guidance of the MMWG and medical experts retained by the Joint Committee, we have assumed that all of these members will be treated and have included a liability for the cost of this treatment. We have valued the liability for other claim payments as if they remained at Level 6 after successful treatment. We assumed there would be no recovery from loss of income or loss of services. We considered 2/3 of the deaths to be HCV-related and 1/3 as not HCV-related.

7.8 HIV Program

190. The Joint Committee has instructed us to assume there will be five additional HIV program claims, occurring every three years starting in 2014, with no additional administration expenses. Each claim will be for $240,000. No interest is paid on these claims and they are not indexed for the cost of living.

7.9 Fees and Expenses

191. We set the assumptions for fees and expenses in consultation with the Joint Committee, taking into account the actual fees and expenses incurred by the Trust, and the budgeted expenses in the near future and the anticipated expenses in subsequent years.

192. In previous valuations the fees and expenses were assumed to continue in the near and medium term, increasing with inflation and then reduce to zero in the long term. For this valuation we have allowed for maturing of the fund by reducing annual costs in proportion to projected number of claimants alive after 2025.

7.10 Effect of Emerging Experience

193. When setting the assumptions for this sufficiency review, we used our best efforts based on our understanding of the Trust. We have also made a number of simplifying assumptions or approximations

in calculating some of the smaller components of the liabilities; in these cases, we have tried to err on the conservative side, i.e. increasing costs and liabilities. There is, however, significant uncertainty with respect to future experience of the fund, especially arising from changes in the medical model and changes in the benefit payments for non-scheduled benefits such as loss of income or loss of services. Differences from our assumptions will continue to emerge over time. These differences and the related actuarial assumptions will continue to be re-examined at each periodic assessment of the Trust.

8 Detailed Results

8.1 Cohort

194. The following table sets out the known cohort, and best estimate and sufficiency assumptions for the unknown cohort, for transfused and hemophiliac claimants:

Summary of Cohort				
	Best Estimate		Sufficiency	
Cohort	Transfused	Hemophiliac	Transfused	Hemophiliac
Known cohort	3,924	1,359	3,924	1,359
Unknown cohort	254	26	254	26
Total claimants	4,178	1,385	4,178	1,385
Total Transfused and Hemophiliac	5,563		5,563	

8.2 Total Liabilities for Transfused and Hemophiliac Claimants

195. The following table sets out the best estimate and sufficiency liabilities for the total (known and unknown) cohort, split between transfused and hemophiliac claimants:

Summary of Total Liabilities for Transfused and Hemophiliac Claimants					
		Best Estimate		Sufficiency	
	Liability - $000s	Transfused	Hemophiliac	Transfused	Hemophiliac
	Co-infected taking $50,000 option		202		202
1.	$10,000 to those alive at 1.1.99	3,082	269	3,082	269
2.	$20,000 if PCR positive at 1.1.99	5,033	538	5,033	538
3.	$30,000 if non-bridging fibrosis	9,726	1,701	12,191	2,169
4.	$65,000 if cirrhosis	12,816	5,510	20,086	8,148
5.	$100,000 if decompensation/cancer	25,210	13,737	33,710	17,115
6.	Loss of income/services in lieu of $30,000 lump sum in 9.1.4	18,103	3,790	19,474	4,148
7.	Loss of income for bridging fibrosis, cirrhosis and decompensation/cancer	17,964	24,491	24,798	28,788
8.	Loss of services for bridging fibrosis, cirrhosis and decompensation/cancer	46,698	28,115	59,387	32,228
9.	Costs of care	17,562	10,362	33,183	18,431
10.	HCV drug therapy	6,606	1,640	7,201	1,790
11.	HCV drug cost	91,183	19,998	123,024	26,841
12.	Uninsured treatment & medication	2,868	3,613	2,948	3,703
13.	Out-of-pocket expenses	4,737	3,237	6,538	4,682
14.	Excess HIV secondarily infected				
15.	Pre-1999 deaths	16,042	27,495	16,207	28,180
16.	Deaths after 1.1.99 - funeral	1,559	762	2,044	918
17.	Deaths after 1.1.99 - loss of support /services	63,698	61,365	73,024	67,310
18.	Loss of guidance, care and companionship	18,318	10,656	23,959	12,827
19.	Claimants with Cryoglobulinemia/Glomerulonephritis	7,889	2,149	7,889	2,149
20.	Known outstanding 2013 payments	6,390	5,521	6,390	5,521
21.	**Total**	**375,482**	**225,153**	**480,167**	**265,957**

8.3 Liability for Expenses

196. The present value of the assumed expenses, as set out in Appendix G, is $ 53,455,000 on the best estimate basis and $ 55,552,000 including the provision for adverse deviation.

8.4 Liability for HIV Program

197. The present value of the assumed claim costs for the HIV program, as set out in section 4.4, is $950,000 on the best estimate basis and $970,000 including the provision for adverse deviation.

8.5 Assets and Liabilities

198. The assets are taken from Section 5.1.

199. The present values of the various compensation amounts set out in Section 4.2 for Transfused and Hemophiliac claimants, as well as the liabilities for the HIV program and Expenses (above) make up the total liabilities.

Assets	**2013**		**2010**
	Best Estimate	**Sufficiency**	**Sufficiency**
Invested Assets	1,028,048	1,028,048	989,775
Provincial/Territorial notional asset	162,152	162,152	187,487
Total Assets	**1,190,199**	**1,190,199**	**1,177,262**
Liabilities			
Transfused	375,482	480,167	662,772
Hemophiliac	225,153	265,957	318,039
HIV Program	950	970	1,100
Expenses	53,455	55,552	34,986
Total Liabilities	**655,040**	**802,646**	**1,016,897**
Excess of Assets over Liabilities	**535,160**	**387,554**	**160,365**

200. The foregoing table indicates that, as at December 31, 2013, the total assets exceed the total sufficiency liabilities by about $387,554.

8.6 Provisions for Adverse Deviations

Provision for Adverse Deviation Included in Sufficiency Liability ($ millions)					
	Total	**Transfused**	**Hemo**	**HIV Program**	**Expenses**
Best Estimate Liability	**655**	**375**	**225**	**1**	**54**
Reduce discount rate to 1.05%	16	8	6	0	2
Reduce treatment efficacy to 80%	65	47	18	0	0
Increase treatment costs to $110,000	39	32	7	0	0
Increase drug therapy to 14.5 weeks	1	1	0	0	0
Lower LOI/LOS recovery rates on clearing virus	4	3	1	0	0
Cost of Care	17	11	6	0	0
Out of pocket expenses after clearing virus	3	1	2	0	0
Margins on LOI/LOS/SRV	3	2	1	0	0
Sufficiency Liability	**803**	**480**	**266**	**1**	**56**
Total Provision	**148**	**105**	**41**	**0**	**2**
Provision %	**23%**	**28%**	**18%**	**2%**	**4%**

201. The foregoing table indicates that the total provision for adverse deviation is $148 million, or about 23% of the best estimate liability. In our opinion, this is appropriate for assessing the sufficiency of the HCV Trust.

8.7 Analysis of Change in Excess Assets

202. We have analyzed the change in the excess asset position approximately as follows:

Summary of Change in Excess Assets	$ millions
Restated excess assets as at December 31, 2010	**160**
Interest on revised excess assets	14
Investment Gain	22
Three year experience gain (loss)	14
Cohort Change	17
Medical model change	370
New drug cost	(146)
Medical model 80% efficacy rate	(65)
Assumption changes	27
Change in methodology for fees and expenses	(25)
Excess assets as at December 31, 2013	**388**

203. The sufficiency of the trust is significantly improved since 2010.

204. The excess assets would have been expected to grow with the assumed investment return, hence the $14 million increase shown above.

205. The actual investment returns, net of inflation, over the three years since the 2010 assessment exceeded the assumed return of 1.05% per year. This resulted in the financial position improving by $22 million.

206. The actual experience over the three years since the 2010 assessment was different to that assumed in 2010. We estimate the net impact of this to be a saving of $14 million.

207. The cohort size is smaller than that assumed in 2010 and as a result the liability is $17 million lower.

208. While the design of the 2013 MMWG model is essentially the same as previous versions, the expected outcomes are significantly different from the prior MMWG models. It is based on historical data, but also takes into account a number of new treatment protocols, as well as certain promising drug therapies that were "fast-tracked" through the Health Canada approval process. These new drug therapies are expected to be provided to a much larger proportion of the claimants than the therapies taken into account in the 2010 model and their efficacy is significantly higher. As a result the HCV prognosis is significantly better than that shown in previous models. A significant proportion of claimants are projected to clear the virus following treatment with these new drugs. The impact of the improved prognosis on the financial outcome is significant and resulted in a reduction of the liability of $370 million.

209. Offsetting this, the cost of the new therapies is very high and the corresponding liability for future treatment is now significant. This increased the liability by $146 million.

210. Due to uncertainty as to the eventual true efficacy of the new treatments, we added a margin for adverse deviations to the treatment efficacy assumption by assuming that the eventual efficacy would be 80% of that assumed by the MMWG. This increased the sufficiency liability by $65 million.

211. The net impact of the improved treatment outcomes, after allowing for the increased treatment cost and some conservatism regarding to the eventual treatment efficacy is still significant, a net reduction in liability of $159 million.

212. In previous valuations the fees and expenses were assumed to continue in the near to medium term, increasing with inflation and then reduce to zero in the long term. For this valuation we have allowed for maturing of the fund by reducing annual costs in proportion to projected number of claimants alive after 2025. This change in methodology resulted in a decrease in excess assets of about $25 million.

213. Finally, the net effect of the remaining assumption changes is a $27 million increase in excess assets.

9 Required Capital

214. The liabilities include some margin for adverse deviation, as discussed earlier in this report. There is, however, significant uncertainty with respect to future experience of the fund that is not provided for in the liability calculation. While the volatility of the financial position arising from changes in the cohort is expected to be much smaller than it was prior to June 30, 2010, the fund is still subject to volatility arising from other factors, in particular, to changes in the medical model (including the impact of the promising new treatments), to investment experience, and to changes in the expected benefit payments for non-scheduled benefits such as loss of income or loss of services.

215. In the event that the fund assets are not sufficient to fund the promised benefits, there are no additional sources of funds. Claimants cannot turn to capital markets to raise additional funds. The risk to the claimants is asymmetrical: if the ultimate experience of the fund is such that there is money left over, each claimant will have received the promised benefit, but if the opposite occurs, later claimants may receive far less than the Agreements specify.

216. In our view, these are compelling reasons for developing a framework, specific to the Hepatitis C fund, to methodically assess what additional buffer (in excess of the sufficiency liability) would be appropriate. We refer to this additional buffer as "required capital" representing the amount of assets, over and above those required to meet the liabilities, that is to be used for the protection, and benefit, of claimants. Our methodology is consistent with the approach we took in the 2010 assessment, when we first implemented a Hepatitis C specific required capital framework by borrowing concepts from the regulation of life insurance companies in Canada, and adapting them as appropriate for the Trust.

217. To develop a Hepatitis C specific framework for the fund, we have examined each significant risk factor, using statistical analysis where possible i.e. we assess the amount of additional assets are needed to ensure the fund can withstand adverse experience with a probability of "x", where "x" is an acceptably high probability, but less than 100%.

218. While a high probability threshold, such as 99%, clearly indicates more security for the fund, there are some practical difficulties in developing a complete and fully integrated statistical model. We have therefore assessed the sensitivity of the fund to each material risk separately and added the results to obtain the total risk amount. This approach effectively assumes that the risk parameters are co-related and that all experience is adverse simultaneously; the probability of this occurring is extremely low. To mitigate the potential overstatement of risk exposure, we have used a 95% probability threshold in our analysis.

219. In summary, we seek to calculate the amount of assets that, taking into account the variability and uncertainty of the future benefit payments and investment returns, are associated with a 95% probability of being sufficient – this is referred to in actuarial literature as the "95% quantile" liability. The difference between this 95% quantile liability and the actual liability reported in the balance sheet becomes the required capital risk amount. Therefore, to the extent there are margins for adverse deviation in the actual liability calculation, the impact is to reduce the additional required capital. Conversely, if there is no margin in the actual liability (i.e. it is a "best estimate" liability), the required capital would be higher. This approach prevents inappropriate duplication (between the actual liability and the required capital) in providing for uncertainty.

220. The ideal way to calculate the assets needed to attain the 95% quantile liability is to use stochastic modeling. In the context of the Hepatitis C fund, stochastic models are available and appropriate for some risks, such as asset default and market risk, and disease progression, but not for all risks i.e. drug efficacy risk, the risk that the amounts claimed for benefits such as loss of income or out-of-pocket expenses will be higher than expected, or that the cohort of approved claimants is larger than anticipated. In these types of risk, we have looked at the variability of actual experience to develop the risk requirement; the logic being that, if we have observed a given level of volatility or uncertainty in the past, it could plausibly occur again.

9.1 Investment Risk

221. Most benefits are indexed to changes in the Consumer Price Index, and so the fund is sensitive to the real rate of investment earnings.

222. Taking into account the asset mix of the Hepatitis C fund, and combined with long term assumptions regarding asset class mean returns, standard deviations, and correlations, we have stochastically produced a distribution of nominal fund returns. As described elsewhere in this report, we used the mean of this distribution (expected return) to develop the best estimate and sufficiency discount rates. The nominal interest rate at the 95th quantile at the low end of the distribution is 2.30% (after rounding to the nearest 5 bps); we select the low end of the distribution because in general, this is more detrimental to the fund's financial position. The corresponding inflation rate was assumed to be 2.00%, giving a real rate of return of about 0.30%.

223. If the fund earned a real rate of return of only 0.30% p.a. for three years, the investment loss (measured relative to the liability discount rate) would be about $25.4 million.

9.2 Interest Mismatch

224. In our report on the 2010 sufficiency, we reported that the duration of the liabilities[1] was about 14.1 years (using a 1.05% net discount rate), while the duration of the assets was shorter. The larger the duration, the greater the sensitivity to interest rate shifts. This means that, at the time of the 2010 assessment, the fund was sensitive to a drop in interest rates, as the resulting increase in liabilities would be more than the increase in asset value.

225. With the significant impact of the new HCV treatments, and the associated drug costs in the five years following the valuation date, the duration of the liabilities as measured in the 2013 assessment has shortened considerably, to about 9.5 years (using a 1.05% net discount rate). At the same time, the duration of the interest-sensitive assets (in particular, the real return bonds) has lengthened, with average duration now about 13.4 years. This means that the fund is now sensitive to an increase in interest rates, as the resulting decrease in liabilities would be less than the decrease in asset value.

226. We have calculated that, if medium to long-term interest rates increased by 0.5%, the market value of the assets would decrease by about $56.8 million, while the liabilities would decrease by about $38.2 million, for a reduction in excess assets of $18.6 million. The 0.5% shift was the same as was used in the 2010 assessment; the current low interest environment suggests that there may be limited downside potential and so the upward shift seems appropriate. We believe this is a reasonable provision for interest mismatch risk as measured in this sufficiency assessment.

227. To the extent that the actual benefits and expenses payable under the HCV arrangement differ from those assumed in the valuation, interest mismatch may exist even if the duration of the assets is set equal to the duration of the liabilities, but it is not possible to quantify this in any meaningful way.

9.3 Efficacy Rate of New HCV Treatments

228. In the interval since the 2010 sufficiency review, there have been dramatic developments in the drugs available to treat HCV. More claimants can be treated by these new drugs, they are tolerated far more easily, and clinical trials indicate cure rates as high as 95%.

229. The impact of incorporating these new drug treatment options into the medical model (and our valuation) resulted in a net reduction of liability. As discussed earlier in this report, because the drugs are so new, we believe there is the potential for variability in their effectiveness: this variability could arise from a number of sources: fewer claimants than expected able to be treated, unexpected drug toxicity

[1] As noted earlier, duration is the weighted average term of the cash flows associated with an asset or a liability. Since it is the average term, some cash flows will occur earlier, and some later, than the duration.

results in drugs being pulled from market, and/or the actual efficacy (cure) rate is lower than anticipated based on the clinical trials.

230. We have included a provision for adverse deviation for drug efficacy in our sufficiency liability by multiplying the best estimate drug efficacy rate by a factor of 80%. Given the newness of these drugs, and the sensitivity of the liability to this assumption, we have calculated an additional buffer for drug efficacy, equal to the increase in liabilities if we substituted a factor of 67% for the 80% factor in the liability calculation. The resulting additional buffer for drug efficacy is $32.6 million for transfused claimants and $12.2 million for hemophiliac claimants, for a total of $44.8 million.

231. Calculating the additional buffer in this way ensures that there is no double counting, since the provision for adverse deviation for drug efficacy in the actuarial liability is excluded from the additional buffer.

9.4 Transition Probability Parameter Uncertainty

232. As noted earlier, the MMWG cannot know with certainty what the actual transition probabilities are, and have provided the estimated mean, associated distribution, and 95% confidence intervals for each one. The estimated mean represents the best estimate of the true value of the transition probability, and the 95% confidence interval indicates that the MMWG are 95% confident (statistically) that the true value falls in the range.

233. We modified our liability calculation to use the distribution specified by the MMWG, rather than the mean of the distribution, for seven[1] key disease transition parameters. Using these distributions in the Tree-age software, we carried out stochastic analysis of the impact of medical parameter uncertainty.

234. Based on the results of 1,000 stochastic scenarios, we determined the distribution of liability results, and selected the liability at the 95% quantile threshold. The difference between the 95% quantile liability and the mean liability (which formed the basis for the sufficiency liability) represents the required capital for this risk exposure.

235. The difference between the 95% quantile liability for parameter uncertainty and the mean liability is $17.3 million for transfused claimants and $11.1 million for hemophiliac claimants, for a total of $28.4 million in additional buffer.

[1] The stochastic analysis was restricted to seven parameters to limit the changes needed to Tree-age. The seven specific parameters chosen were those that we understand will have the most significant impact on the results.

9.5 Statistical Variation in Each Claimant's Progression Through the Disease

236. In our 2010 report, we incorporated a specific buffer for statistical variation in each claimant's progression through disease stages. The rationale for this buffer was the statement by the MMWG that there are slow, medium and fast progressors through the disease.

237. With the passage of time, it is reasonable to believe that at least some of the fast progressors are no longer alive, and that the alive cohort is more heavily weighted to the slow and medium progressors.

238. Furthermore, with the advent of the new drug treatments, and the high cure rates (even after applying the 80% factor to the MMWG best estimates), we believe the significance statistical variation in each claimant's progression through the disease is reduced.

239. We have therefore dropped this component from the buffer; it is effectively replaced by the drug efficacy rate component.

9.6 Uncertainty Regarding Other Benefit and Claim Amounts

240. For benefits other than the lump sums, the dollar amount of benefits that will be paid in the future is not known.

241. Ignoring for the moment the four claimants who exceeded the $300,000 cap, the average loss of income payment in each year has remained reasonably stable, despite the individual variation. There have, however, been four claimants whose pre-claim income exceeded the $300,000 cap on loss of income benefits (one claimant's pre-claim income was about $2 million annually); initially three had their benefits limited by the cap, but this cap was lifted and these claimants received (or are receiving) the full benefit defined in the Agreements, with no limit. It is statistically unlikely that another very large loss of income claim will be submitted, but in the event that one does, our understanding is that the full amount would be paid if that would not impair the overall fund sufficiency. It seems reasonable to earmark some amount for this potential future claim; a $1 million annual loss of income claim payable for 12 years would require about $11.3 million in assets.

242. Other benefits also have significant variation in individual payments, in particular the costs of care, uninsured treatment and medication, drug therapy, and out-of-pocket expenses. For example, based on a review of the 2013 data, the average out-of-pocket claim was just under $2000, but the actual payments ranged from about $2 to over $34,000. There is also wide variation in claim amounts for costs of care. We have incorporated a specific provision for adverse deviation in the sufficiency liability for costs of care, and out-of-pocket expense claims for those claimants who clear the virus, and therefore believe an additional buffer for these benefits is not warranted. Similarly, we have incorporated a specific

provision for adverse deviation for the drug therapy duration and the cost of HCV treatment drugs, and so no additional buffer is required.

243. Our valuation incorporates an assumption regarding the proportion of deaths (other than deaths at level 6) that are deemed to be HCV related (with the ensuing additional benefits). There is considerable uncertainty around this outcome, as it depends on a number of factors, including the co-morbidities and the interpretation of "death materially contributed to by HCV". If the assumed proportion of deaths at levels 2 through 5 that are deemed to be caused by HCV were increased by adding 10% at each level, the liability would increase by $17.4 million.

244. Considering only this subset (one additional large loss of income claim and additional deaths attributed to HCV) of the possible variation in benefit and claim amounts, and calculating the impact of a plausible change in average benefit amount or claim rate for each gives a total increase in liability of $28.7 million. We believe this is a reasonable risk amount in respect of benefit uncertainty.

9.7 Actual Size of Unknown Cohort

245. Although the official cut-off date for claimants coming forward was 30 June 2010, there is still some uncertainty regarding the size (and profile) of the unknown cohort: additional claimants may be approved due to unusual circumstances and/or the assumed denial rate could prove to be too high. If 25 additional unknown alive transfused claimants were approved, the liability would increase by about $5.3 million. The 25 additional unknowns represents two types of uncertainty: the possibility that the number for claimants coming forward in the future is higher than anticipated (we assumed there were 10 unanticipated claimants) and the risk that the assumed denial rate applied to the claims in process and/or CAP1 and CAP2 claims higher than actual (in which case we assumed an additional 15 claimants would be approved).

9.8 Results of Hepatitis C Specific Approach to Required Capital

246. The results of the Hepatitis C specific approach to calculating required capital are set out in the following table:

Estimated Required Capital on Hepatitis C Specific Approach		
Risk Component		**Hepatitis C Specific Risk Amount ($ millions)**
Investment Risk		$25.4
Mismatch Risk		18.6
Claimant Risk	Drug Treatment Efficacy	44.8
	Parameter Uncertainty	28.4
	Benefit Amount Uncertainty	28.7
	Cohort Uncertainty	5.3
Total Required Capital		151.2
Required Capital as a percentage of the Sufficiency Liability		18.8%

10 Financial Position

247. The following table summarizes the financial position of the Trust as at December 31, 2013 and 2010.

Assets	2013		2010
	Best Estimate	Sufficiency	Sufficiency
Invested Assets	1,028,048	1,028,048	989,775
Provincial/Territorial notional asset	162,152	162,152	187,487
Total Assets	**1,190,199**	**1,190,199**	**1,177,262**
Liabilities			
Transfused	375,482	480,167	662,772
Hemophiliac	225,153	265,957	318,039
HIV Program	950	970	1,100
Expenses	53,455	55,552	34,986
Total Liabilities	**655,040**	**802,646**	**1,016,897**
Excess of Assets over Liabilities	535,160	387,554	160,365
Required Capital	n/a	151,213	159,500
Excess Capital	**n/a**	**236,341**	**865**

248. The foregoing table indicates that, as at December 31, 2013 the assets exceed the sufficiency liabilities by about $387,554,000.

249. After allowing for the required capital buffer of $151,213,000 as discussed in Section 9, the excess capital is $236,341,000.

11 Sensitivity Tests

11.1 Net Discount Rate

250. The sufficiency liability calculations are based on a sufficiency net discount rate of 1.05% per annum. In order to illustrate the sensitivity of the results to variations in the investment experience, and hence in the valuation net discount rate, calculations have also been done at net discount rates of 1.30% per annum (this reduces the present value of the liabilities) and 0.80% per annum (this increases the present value of the liabilities).

251. The impact on the total sufficiency liabilities is as follows:

	($ millions)		
	Liabilities	Impact on Liabilities	
	@ 1.05% p.a.	@ 1.30% p.a.	@ 0.80% p.a.
Transfused Plan	480.2	- 10.3	+ 11.0
Hemophiliac Plan	265.9	- 6.3	+ 6.7
HIV Program	1.0	- 0.0	+ 0.0
Total benefits	747.1	- 16.6	+ 17.7
Expenses	55.5	- 2.1	+ 2.3
Total sufficiency liabilities	802.6	- 18.7	+ 20.0

11.2 Cohort Size

252. The table below shows the liability for the unknown cohort alive at January 1, 1999, and for an additional 10 approved alive claimants, separately for transfused and hemophiliac.

Unknown cohort Alive at January 1, 1999	Transfused Plan Liability ($ millions)	Hemophiliac Plan Liability ($ millions)
Sufficiency liability for unknowns alive at January 1, 1999	48.8	7.9
+/- each 10 persons	+/-2.1	+/-3.4

11.3 CAP 3

253. We were asked to calculate the liability for CAP3 and report it as a sensitivity, not included in the sufficiency liability amount. We have assumed that 120 transfused and 10 hemophiliac claims will be made and approved under CAP3 and that none of these claims will be DB9s. Taking into account the unknown alive and DA9 sensitivity results report above, we calculate the resulting CAP3 liability to be $29.0 million, $25.6 million for transfused and $3.4 million for hemophiliac.

11.4 HCV Drug Therapy

254. HCV Drug Therapy payments are made to claimants receiving a drug treatment regimen that includes ribavirin or interferon. Prior to the emergence of the recent HCV treatment drugs, all HCV treatments incorporated one or both of these drugs. The most recent drug regimens, which were approved after development of the medical model, may not include these drugs; however, in the calculation of our sufficiency liability, we have assumed that Drug Therapy payments will be made to all claimants receiving HCV drug treatment for the duration of their treatment.

255. To provide insight into the effect of potential overstatement of the liability as a result of this assumption, the following table shows the impact of reducing the number of claimants for future HCV drug therapy payments by 50%. The assumption regarding past payments for Drug Therapy claims incurred before December 31, 2013 (under the older drug regimens) is held constant:

Sensitivity to HCV Drug Therapy Assumption for Transfused and Hemophiliac Claimants $000s		
	Transfused	**Hemophiliac**
Sufficiency Liability	7,201	1,790
Liability if future HCV Drug Therapy payments are reduced by 50%	3,737	906

256. As shown above, reducing the number of claimants receiving Drug Therapy would reduce the liability by $3,464,000 (= $7,201,000 - $3,737,000) for Transfused and $884,000 (=$1,790,000 - $906,000). This is not material in the context of the total liabilities of the Trust.

12 Comparison with the Morneau Shepell Calculations

257. The assumptions for the best estimate valuation and the sufficiency valuation have been developed in conjunction with Morneau Shepell. As a result, no differences in the financial results arise as a result of assumption differences.

258. The actuarial models employed by Morneau Shepell and Eckler are quite different. As discussed previously, the Eckler model is a stochastic model that has been developed by adding financial overlay to the MMWG Treeage Pro medical model. The Morneau Shepell model is a deterministic model (i.e. it doesn't incorporate statistical variability into the liability calculation) that Morneau Shepell independently developed to reflect the disease progression described in the MMWG medical model. Eckler and Morneau Shepell spent a considerable amount of time reconciling the results of the two different financial models. Refinements were made to both models to ensure consistency of results.

259. The two models produce substantially the same results, both on a Best Estimate and on a Sufficiency basis. Not surprisingly there is a small residual difference between the two models, but the difference of about $10 million or 1.24%, is well within an acceptable range.

260. Both Eckler and Morneau Shepell agree that it is appropriate to hold assets in excess of the liabilities (referred to by Eckler as required capital). Our views on what is an acceptable additional buffer are slightly different, but both are within the range of acceptable outcomes. When the total financial result is computed, the net difference in the excess assets is small (Morneau Shepell has a slightly higher liability and slightly lower buffer, compared to Eckler with a slightly lower liability and slightly higher buffer).

13 Opinion

In our opinion,

(a) the Trust funds are sufficient to meet the liabilities of the Trust,

(b) the claimant data on which the valuation is based are sufficient and reliable for the purposes of the valuation,

(c) the assumptions are appropriate for the purposes of the valuation, and

(d) the methods employed in the valuation are appropriate for the purposes of the valuation.

This report has been prepared, and our opinions given, in accordance with accepted actuarial practice in Canada. Pursuant to the requirements of the settlement agreement, the next valuation should be completed no later than as of December 31, 2016.

To the best of our knowledge, there are no material subsequent events that would affect the results and recommendations of this valuation. Any investment experience occurring between the valuation date and the report date, which differs from the assumption made, is not reflected in this report and will be reported on in future valuations.

On behalf of the Eckler actuarial personnel who worked on this report, we certify that we are aware that our duties are:

(a) to provide opinion evidence that is fair, objective and non-partisan and related only to matters within our area of expertise; and

(b) to assist the court and provide such additional assistance as the court may reasonably require to determine a matter in issue.

We are aware that the foregoing duties prevail over any obligation they may owe to any party on whose behalf we are engaged and we are aware that we are not to be an advocate for any party. We confirm that the report conforms with the above-noted duties. We further confirm that if called upon to give oral or written testimony, we will give such testimony in conformity with these duties.

Richard A. Border
Fellow of the Canadian Institute of Actuaries[1]
Fellow of the Institute and Faculty of Actuaries

Wendy F. Harrison
Fellow of the Canadian Institute of Actuaries
Fellow of the Society of Actuaries

[1] Canadian Institute of Actuaries is the Primary Regulator.

Appendix A – Data

Source of Data

261. The seriatim information with respect to claimants as at December 31, 2013 was provided by the administrator through the Joint Committee. For each known claimant, the data included dozens of data fields, including unique claimant identifier, whether transfused or hemophiliac, gender, date of birth, date of death if applicable, disease level, etc. Additional files including a history of all benefit payments (by benefit type e.g. out-of-pocket or loss if income) made from the trust, details on previous drug treatments, and information on claims submitted but not approved were provided by the administrator through the Joint Committee.

Data Checks

262. We reviewed the data and subjected it to a number of tests of reasonableness and consistency, including reconciliation of claimant count to the 2010 data; consistency between data fields (such as previous drug therapy claim and previous treatment flag); and consistency of the approved and denied cohort between different data files. In cases of apparent inconsistency, we asked for and received clarification from the administrator, through the Joint Committee. We also make cohort adjustments according to the response from the administrator.

A-1 Transfused Known Claimants by Count[1]

Distribution of those alive by stage at December 31, 2013								
Age at Dec-31-13	Number alive at Dec-31-13	Level 1 Cleared virus	Level 2 PCR positive	Level 3 Non-bridging fibrosis	Level 4 Bridging fibrosis	Level 5 Cirrhosis	Level 6 Decomp/ cancer/ transplant/ lymphoma	Level 6 Glom/ Cryo
0-19	3	0	3	0	0	0	0	0
20-29	188	30	66	76	7	4	2	3
30-39	118	27	34	45	6	5	1	0
40-49	372	65	92	178	16	13	5	3
50-59	685	129	184	260	56	32	20	4
60-69	492	81	131	172	39	42	19	8
70-79	403	74	148	98	32	36	13	2
80-89	329	64	174	46	18	21	6	0
90+	231	40	161	23	1	5	1	0
Total	**2,821**	**510**	**993**	**898**	**175**	**158**	**67**	**20**

Average age at December 31, 2013: 61.8

A-2 Transfused Known Claimants Distribution

	Distribution of those alive by stage at December 31, 2013							
Age at Dec-31-13	Number alive at Dec-31-13	Level 1 Cleared virus	Level 2 PCR positive	Level 3 Non-bridging fibrosis	Level 4 Bridging fibrosis	Level 5 Cirrhosis	Level 6 Decomp/ cancer/ transplant/ lymphoma	Level 6 Glom/ Cryo
0-19	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
20-29	6.6%	1.1%	2.3%	2.7%	0.2%	0.1%	0.1%	0.1%
30-39	4.2%	1.0%	1.2%	1.6%	0.2%	0.2%	0.0%	0.0%
40-49	13.3%	2.3%	3.3%	6.3%	0.6%	0.5%	0.2%	0.1%
50-59	24.2%	4.6%	6.5%	9.2%	2.0%	1.1%	0.7%	0.1%
60-69	17.5%	2.9%	4.6%	6.1%	1.4%	1.5%	0.7%	0.3%
70-79	14.4%	2.6%	5.3%	3.5%	1.1%	1.3%	0.5%	0.1%
80-89	11.6%	2.3%	6.2%	1.6%	0.6%	0.7%	0.2%	0.0%
90+	8.1%	1.4%	5.7%	0.8%	0.0%	0.2%	0.0%	0.0%
Total	**100.0%**	**18.2%**	**35.2%**	**31.8%**	**6.1%**	**5.6%**	**2.4%**	**0.7%**

[1] Includes secondarily infected claimants.

A-3 Hemophiliac Known Claimants by Count[1]

Distribution of those alive by stage at December 31, 2013									
Age at Dec-31-13	Number alive at Dec-31-13	Level 1 Cleared virus	Level 2 PCR positive	Level 3 Non-bridging fibrosis	Level 4 Bridging fibrosis	Level 5 Cirrhosis	Level 6 Decomp/ cancer/ transplant/ lymphoma	Level 6 Glom/ Cryo	HIV Co-infected
0-19	1	0	1	0	0	0	0	0	0
20-29	16	5	3	7	1	0	0	0	1
30-39	186	52	38	67	12	14	3	0	35
40-49	265	40	55	107	26	23	12	2	71
50-59	216	23	45	83	24	28	11	2	56
60-69	114	14	15	48	11	13	12	1	15
70-79	47	8	12	12	5	4	6	0	2
80-89	24	4	16	1	2	0	1	0	1
90+	8	0	7	1	0	0	0	0	0
Total	**877**	**146**	**192**	**326**	**81**	**82**	**45**	**5**	**181**

Average age at December 31, 2013: 50.2

Included above are 50 HIV co-infected claimants who elected to take the $50K options for whom no further liability remains and who were therefore removed from our model.

A-4 Hemophiliac Known Claimants Distribution

Distribution of those alive by stage at December 31, 2013									
Age at Dec-31-13	Number alive at Dec-31-13	Level 1 Cleared virus	Level 2 PCR positive	Level 3 Non-bridging fibrosis	Level 4 Bridging fibrosis	Level 5 Cirrhosis	Level 6 Decomp/ cancer/ transplant/ lymphoma	Level 6 Glom/ Cryo	HIV Co-infected
0-19	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
20-29	1.8%	0.6%	0.3%	0.8%	0.1%	0.0%	0.0%	0.0%	0.1%
30-39	21.1%	5.9%	4.3%	7.6%	1.4%	1.6%	0.3%	0.0%	4.0%
40-49	30.3%	4.6%	6.3%	12.2%	3.0%	2.6%	1.4%	0.2%	8.1%
50-59	24.6%	2.6%	5.1%	9.5%	2.7%	3.2%	1.3%	0.2%	6.4%
60-69	13.0%	1.6%	1.7%	5.5%	1.2%	1.5%	1.4%	0.1%	1.7%
70-79	5.5%	0.9%	1.4%	1.4%	0.6%	0.5%	0.7%	0.0%	0.2%
80-89	2.7%	0.5%	1.8%	0.1%	0.2%	0.0%	0.1%	0.0%	0.1%
90+	0.9%	0.0%	0.8%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
Total	**100.0%**	**16.7%**	**21.8%**	**37.2%**	**9.2%**	**9.4%**	**5.2%**	**0.5%**	**20.6%**

[1] Includes secondarily infected claimants.

Appendix B – Disease Progression

Summary of Transition Probabilities used in the 2013 HCV Markov Prediction Model

Type of Transition Probability	Mean (best estimate)	Standard deviation
F0 to HCV RNA-	0.017	0.0028
F0 to F1	0.054	0.0041
F1 to F2	0.120	0.0163
F2 to F3	0.135	0.0255
F3 to F4 (Cirrhosis)	0.138	0.0316
F4 (Cirrhosis) to Decompensated Cirrhosis	0.078	0.0026
Decompensated cirrhosis or HCC to Liver transplantation	0.004	0.0001
HCC to death	0.182	0.0074
Liver transplantation to Death (first year)	0.086	0.0380
Liver transplantation to Death (after first year)	0.039	0.0018
Decompensation to liver-related death	0.152	0.0031
F1 to HCC	0.0001	0.0002
F2 to HCC	0.0001	0.0002
F3 to HCC	0.001	0.0022
F4 (Cirrhosis) to HCC	0.025	0.0008
Decompensation to HCC	0.02	0.0008
HCC to transplant	0.004	0.0001

Appendix C – Mortality Assumptions

Mortality Rates

Mortality	Best Estimate	Sufficiency
All causes except HCV	Canada Life Table 2009-2011	Same
All causes except HCV co-infected with HIV	624% of Canada Life Table 2009-2011	Same
Decompensated Cirrhosis	Greater of 15.2% and all cause mortality	Same
HCC	Greater of 18.2% and all cause mortality	Same
Liver transplant – first year	Greater of 8.6% and all cause mortality	Same
Liver transplant – after first year	Greater of 3.9% and all cause mortality	Same
Male / female mix	Actual	Same

HCV Deaths: Percentage of total deaths assumed to be deemed to be HCV related

	Claimants who did not clear virus	Claimants who cleared the virus
Stage 1	0%	0%
Stage 2	10%	0%
Stage 3	35%	0%
Stage 4	45%	25%
Stage 5	80%	60%
Stage 6	100%	100%

The best estimate and sufficiency assumptions are the same for percentage of deaths assumed to be deemed to be HCV related.

Appendix D – Economic Assumptions

2013 Economic Assumptions

Fund	Asset Class	Asset Allocation	Fund Allocation	Total Asset Allocation	Expected Return
Long term Fund			**78.7%**		
	Real Return Bonds	80.0%		62.9%	2.9%
	Universe Bonds	6.0%		4.7%	4.1%
	Canadian Equity	7.0%		5.5%	7.6%
	US Equity	3.5%		2.8%	7.7%
	EAFE Equity	3.5%		2.8%	
Short term Fund			**7.7%**		
	Short term bonds	100.0%		7.7%	4.1%
	Cash	0.0%		0.0%	3.1%
Provincial/territorial Notional Assets	**3 Month Treasury Bills**	**100.0%**	**13.6%**	**13.6%**	**3.1%**

Component of Return	**%**
Weighted Average Return	3.60
Diversification and rebalancing	0.24
Best Estimate Return Gross of investment expenses	3.84
Investment Expenses	(0.04)
Best Estimate Nominal Return	3.80
Best Estimate Nominal Return rounded to nearest 10th%	**3.80**
Best Estimate Inflation	2.50
Best Estimate Net Discount Rate	**1.30**
Margin for Adverse Deviation	0.25
Sufficiency Valuation Net Discount Rate	**1.05**

2010 Economic Assumptions

Best Estimate Nominal Return rounded to nearest 10th%	**3.80%**
Best Estimate Inflation	2.50
Best Estimate Net Discount Rate	**1.30**
Margin for Adverse Deviation	0.25
Sufficiency Valuation Net Discount Rate	**1.05**

Appendix E – Treatment Probabilities and Costs

Treatment and Treatment Efficacies - 2013

	Treatment Naïve without HIV	Treatment Naïve with HIV	Previously Treated without HIV	Previously Treated with HIV
Annual treatment rate first five years	34.0%	19.3%	38.2%	17.5%
Annual treatment rate after five years	0.0%	0.0%	0.0%	0.0%
Cumulative treatment	87.5%	65.8%	91.0%	61.7%
Percentage of treatments using:				
PEG-IFN/RBV	0.0%	0.0%	0.0%	0.0%
PEG-IFN/RBN based triple therapy	14.3%	8.3%	7.1%	8.3%
Sofosbuvir-based doublet	50.0%	25.0%	35.7%	8.3%
3D regimen plus RBV	35.7%	66.7%	57.1%	83.4%
Treatment Efficacy – Best Estimate:				
PEG-IFN/RBV	45.5%	37.1%	37.4%	30.5%
PEG-IFN/RBN based triple therapy	70.0%	73.5%	53.8%	53.8%
Sofosbuvir-based doublet	94.6%	80.2%	95.4%	80.9%
3D regimen plus RBV	96.2%	81.6%	96.3%	81.7%
Treatment Efficacy – Sufficiency	All efficacy rates are 80% of the corresponding Best Estimate			

Treatment Costs

	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Treatment Costs			
PEG-INF/RBC-based triple therapy	Included in uninsured treatment cost assumption	60,000	110,000
Sofosbuvir – based doublets		85,000	110,000
3D regimen plus RBC		85,000	110,000
Percentage of treatment cost met by Fund			
Below age 65		100%	100%
Above age 65		60%	60%

2010 Assumptions

Type of Transition Probability	Best estimate	Valuation (60^{th} percentile)
Effect of HCV treatment		
Annual treatment rate < 65: F0: 0%	0.0000	0.0000
Annual treatment rate < 65: F1-F3: 10% Treatment efficacy (SVR): 49%	0.0490	0.0439
Annual treatment rate < 65: F4: 10% Treatment efficacy (SVR): 31%	0.0310	0.0278
Annual treatment rate > 65: F0: 0%	0.0000	0.0000
Annual treatment rate > 65: F1-F3: 3.3% Treatment efficacy (SVR): 49%	0.0163	0.0145
Annual treatment rate < 65: F4: 3.3% Treatment efficacy (SVR): 31%	0.0103	0.0092
Effect of HIV status on fibrosis progression rates	2.1220	2.2710
Excess mortality associated with HIV infection	624%	658%

Appendix F – Compensation Assumptions

The following tables shows the 1999 base amounts of compensation together with the 2014 indexed figures for amounts specified in the Plan, as well as the assumed payments where the dollar amounts are not specified, as well as other payment related assumptions in cases where not all claimants will receive a payment. All amounts taken into account in the 2013 valuation are in 2014 dollars. We also show in the comparative amounts and assumptions used in the 2010 valuation in 2011 dollars.

Type of Benefits	1999 Original Amount	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Lump sum payments				
Stage 1	$10,000	$12,744	$13,458	Same
Stage 2	20,000	25,488	26,915	Same
Stage 3	30,000	38,233	40,373	Same
Stage 5	65,000	82,838	87,475	Same
Stage 6	100,000	127,442	134,577	Same

Type of Benefits	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Loss of income amounts			
Already in payment	Actual claim	Actual claim	Same
Commencing in the future			
Transfused	35,000	39,000	43,000
Hemophiliac	38,000	48,000	53,000
Percentage claiming Loss of Income (below age 65)			
Already in payment and not cleared virus	100%	100%	Same
Not cleared the virus and commencing in the future			
Stage 3	3%	3%	Same
Stage 4 and 5			
- not yet at stage 4 or 5	18%	21%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	9.8%	5.8%	Same
- hemophiliac	1.6%	3.2%	Same
Stage 6			
- not yet at stage 4, 5 or 6	17%	25%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	13.4%	5.1%	Same
- hemophiliac	9.8%	5.1%	Same
- already stage 6, but not yet claiming			
- transfused	10.5%	0.0%	Same
- hemophiliac	0.0%	0.0%	Same
Cleared the virus and not currently claiming[1]	Same as not cleared virus	0.0%	Same
Cleared virus and currently claiming[1]	Same as not cleared virus	Per recovery rates	

[1] Also applies to loss of services.

Loss of income and loss of services recovery rates	2013 Best Estimate			2013 Sufficiency		
Stage when clearing the virus	3 + 4	5	6	3 + 4	5	6
Duration since claim commenced						
One year	50%	25%	0%	25%	13%	0%
Two years	30%	15%	0%	15%	8%	0%
Three years	25%	13%	0%	13%	7%	0%
Four years	25%	13%	0%	13%	7%	0%
Five years	15%	8%	0%	8%	4%	0%
Six years	10%	5%	0%	5%	3%	0%
Seven years	5%	3%	0%	3%	2%	0%
Eight years	5%	3%	0%	3%	1%	0%
Nine or more years	0%	0%	0%	0%	0%	0%

Type of Benefits	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Loss of services amounts			
Transfused and Hemophiliacs	15,000	16,000	Same
Percentage claiming Loss of Services (below age 65)			
Stage 3	2%	2%	Same
Stage 4 and 5			
- not yet at stage 4 or 5	39%	30%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	21.2%	6.7%	Same
- hemophiliac	3.5%	0.0%	Same
Stage 6			
- not yet at stage 4, 5 or 6	57%	40%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	44.9%	14.3%	Same
- hemophiliac	32.9%	14.3%	Same
- already stage 6, but not yet claiming			
- transfused	35.2%	5.3%	Same
- hemophiliac	0.0%	0.0%	Same
Percentage claiming Loss of Services (above age 64)			
Stage 3	5%	7%	Same
Stage 4 and 5			
- not yet at stage 4 or 5	57%	51%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	30.9%	27.3%	Same
- hemophiliac	5.2%	0.0%	Same
Stage 6			
- not yet at stage 4, 5 or 6	74%	65%	Same
- already stage 4 or 5, but not yet claiming			
- transfused	58.2%	28.6%	Same
- hemophiliac	42.7%	28.6%	Same
- already stage 6, but not yet claiming			
- transfused	45.6%	40.9%	Same
- hemophiliac	0.0%	0.0%	Same

Type of Benefits	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Costs of care – Stage 6 only			
Average amount	$21,000	30,000	45,000
Percentage claiming	15%	40%	Same
HCV drug therapy			
Compensation per month	$1,274	$1,346	Same
Treatment month	11	3.3	3.6
Percentage claiming	65% at stage 2 or worse	100% of claimants being treated	Same
Uninsured treatment and medication for those who have not cleared the virus			
Transfused	$3,000	$1,500	Same
Hemo	$4,000	$3,000	Same
Stage 2 or worse - Transfused	4%	4.5%	Same
Stage 2 or worse - Hemo	7%	7.5%	Same
Uninsured treatment and medication for treatment to clear the virus	Included above	Appendix E	Appendix E
Out of pocket expenses – not cleared virus			
Transfused	$1,700	$1,800	Same
Hemo	$2,500	$2,600	Same
Percentage of people will claim	12%	8%	Same
Out of pocket expenses – present value of all payments to those who have cleared the virus			
Transfused		1,200	2,400
Hemo		5,000	10,000
Percentage of people will claim		All, at date assumed cleared	Same
HIV Program	6 additional claims at $240,000 per claim	5 additional claims at $240,000 per claim	Same

Type of Benefits	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Payments related to all deaths			
Assumed funeral costs	$5,000	$4,300	Same
Deaths before January 1, 1999			
$50K option	$63,721	$67,289	Same
Five knowns who chose $50K option, but whose payments to date are less than $120K		Total extra liability = $500,000	Same
$120K option	$152,931	$161,493	Same
Co-infected taking $72K option - Hemo	$91,759	$96,896	Same
Payment to family - Transfused	$70,000	$75,000	Same
Payment to family - Hemo	$80,000	$85,000	Same
Loss of services	$15,000	$16,000	Same
Loss of support - Transfused	$30,000	$30,000	$34,000
Loss of support - Hemo	$32,000	$34,000	$36,000
Percentage electing $50K option	52%	52%	Same
Percentage electing $120K option	48%	48%	Same
Of those electing the $50K option (%)			Same
Loss of support - Transfused	20%	20%	Same
Loss of services - Transfused	80%	80%	Same
Loss of support - Hemo	50%	50%	Same
Loss of services - Hemo	50%	50%	Same

Type of Benefits	2010 Valuation	2013 Best Estimate	2013 Sufficiency
Deaths after January 1, 1999			
Loss of support where loss of income was being paid	Same as below	70% of loss of income	Same
Loss of support where income loss was not being paid - Transfused	$30,000	$31,000	$34,000
Loss of support where income loss was not being paid – Hemo	$32,000	$33,000	$36,000
Loss of services	$15,000	$16,000	Same
Of those DA9 deaths caused by HCV			
Percent claiming where loss of income or loss of service is already being paid	Same as below	100%	Same
Percent claiming where loss of income or loss of service is not being paid			
Loss of support (younger than age 65)	10%	45%	Same
Loss of service (younger than age 65)	40%	5%	Same
Loss of service (older than age 65)	50%	40%	Same
Total care/guidance - Transfused	$55,000	$50,000	Same
Total care/guidance - Hemo	$55,000	$60,000	Same

Appendix G – Expense Assumptions and Liability

263. In prior years, the Joint Committee provided the assumptions regarding fees and expenses payable by the fund. For the 2013 Financial Sufficiency Review, we developed the expense assumptions, with reference to:

- Discussion with the Joint Committee
- Actual expenses incurred in the recent past;
- Budgeted expenses for the near future, if applicable.

264. Some expenses are on a three year cycle to reflect the extra costs associated with triennial sufficiency reviews.

265. In prior years, the expenses were assumed to be payable to a specific point in the future; for the 2010 review, that was 18 years following the review date. For the 2013 Financial Sufficiency Review, the methodology was modified to project the expenses over a longer period of time, reflecting the projected run-off of the program. With the new drug treatments, which have much higher cure rates than the older treatments, claimants are projected to live longer; this has been reflected in the expense assumptions as follows.

266. We have allowed for the maturing of the fund, by reducing annual costs in proportion to projected number of claimants alive after 2026 as per the MMWG report. Specifically, the expenses are projected by major category based on budgeted amounts, direction from the Joint Committee, and in some cases, trend, from 2014 to 2025. Starting in 2026, the amounts that would otherwise be projected are reduced in proportion to the year by year change in the proportion of claimants that are "known alive" at the review projected by the medical model to still be alive at the future year, e.g., of the known alive claimants at the review date, 77.1% are projected to be alive in 2025 and 74.9% are projected to be alive in 2026, a reduction of about 3% (.749/.771 - 1). The 2026 expenses are therefore projected to be 3% lower than 2025. For claims that occur on a three year cycle (related to sufficiency reviews), the proportions are adjusted accordingly.

267. The proportion of alive claimants was set out in table 13.1 of the 2013 MMWG report, dated September 2014. These proportions are projected and reported at 10 year intervals. We interpolated linearly for the intermediate years. After 50 years, about 10% of the claimants are still alive. We truncated the projection at 50 years, since the present value of expenses beyond that date would not be material to the results of the valuation.

268. If we had truncated the projection of expenses after 40 years instead of 50, the liability for expenses would be $52.9 million, or $2.6 million lower than the liability that we calculated.

269. While some expenses are expected to trend down in proportion to the number of alive claimants, other expenses (e.g. those associated with the sufficiency reviews) are not necessarily proportionate to the remaining alive cohort. By 2025, however, we expect that much of the uncertainty and variability around the medical model and the expected disease progression of the claimants will be reduced, and that the cost of carrying out a triennial sufficiency review could decrease. It is difficult to be precise with the projection of these expenses decades into the future, but we believe that the approach we have taken is reasonable.

270. This methodology is based on the premise that the HCV program continues on a going concern basis until all benefits due to claimants have been paid. If the fund were to be wound up at some point prior to that point, significant windup expenses would be incurred; these wind-up expenses could be considered as an acceleration of the expenses projected under the going concern scenario. In this way, the methodology adopted for the 2013 review also encompasses the alternate scenario of wind up.

271. Goods and services tax/harmonized sales tax (GST/HST) are applied to each expense category based on a weighted average across the applicable provinces.

272. The dollar references are in 2014 dollars. We have allowed for inflation by discounting at the net discount rate of 1.3% for best estimate and 1.05% for sufficiency liabilities.

273. The only difference between the best estimate and the sufficiency liability is the effect of the different discount rates for these two liabilities.

274. The specific expenses are set out below:

275. Actuarial Financial Sufficiency Review (5% HST for BC)

(a) $407,000 in 2014 for financial sufficiency; $490,000 in 2015 for financial sufficiency report preparation and response; $50,000 in 2016; then start three year cycle of $500,000 following review date, $200,000 the following year, and $50,000 in the third year; this three year cycle continues to 2025; grading off thereafter as described above.

276. Actuarial Regular (5% HST for BC)

(b) $29,000 in 2014 based on actual, $50,000 per year for actuarial and investment advice to 2025; plus $25,000 for special projects every third year, starting in 2016, to 2025; grading off thereafter as described above.

277. Accounting Expert Testimony and Assistance (13% HST for Ontario)

(c) $20,000 per year until 2020; $15,000 per year from 2021 to 2025; grading off thereafter as described above.

278. Administration (13% HST for Ontario)

(d) $740,000 for 2014; $639,000 in 2015; $623,000 in 2016; $600,000 from 2017 to 2025; grading off thereafter as described above.

279. Class Member Communication (13% HST for Ontario)

(e) $50,000 every third year, starting in 2014, to 2025; grading off thereafter as described above.

280. Arbitrators/Referees (11.49% blended HST/GST and QST for BC, Ontario and Quebec)

(f) $20,000 per year through 2017; $15,000 in 2018; $10,000 per year from 2019 to 2025; grading off thereafter as described above.

281. Audit (13% HST for Ontario)

(g) $92,000 per year for audit activities and preparation of financial statements from 2014 to 2025; plus $25,000 for special projects every third year, starting in 2016, to 2025; grading off thereafter as described above.

282. Canadian Blood Services (No HST or GST)

(h) $10,000 per year to 2025; grading off thereafter as described above.

283. Fund Counsel (11.49% blended HST/GST and QST for BC, Ontario and Quebec)

(j) $90,000 per year until 2017, declining thereafter $9,000 per year until it reaches $45,000; $45,000 per year until 2025; grading off thereafter as described above.

284. Héma-Québec (No HST or GST)

(k) $3,000 per year to 2025; grading off thereafter as described above.

285. Independent Counsel (13% HST for Ontario)

(l) $10,000 per year to 2025; grading off thereafter as described above.

286. Joint Committee Financial Sufficiency Review (10.39% blended HST/GST and QST for BC, Ontario and Quebec)

(m) $330,000 for financial sufficiency in 2014; $800,000 in 2015; $100,000 in 2016; then start three year cycle $300,000 following review date, $200,000 the following year, and $100,000 in the third year; this three year cycle continues to 2025; grading off thereafter as described above.

287. Joint Committee Financial Administration (10.39% blended HST/GST and QST for BC, Ontario and Quebec)

(n) $580,000 for general oversight of the ongoing administration in 2014 based on actual; $650,000 in 2015 based on budget; declining after 2015 by $50,000 per year until it reaches $400,000; $400,000 per year until 2025; grading off thereafter as described above.

288. Medical Modelling (No HST or GST)

(o) $220,000 in 2014, and every third year thereafter until 2025; grading off thereafter as described above.

289. Monitor (13% HST for Ontario)

(p) $60,000 per year until 2017; declining thereafter $6,000 per year until it reaches $30,000; $30,000 per year until 2025, grading off thereafter as described above.

290. Software Development (13% HST for Ontario)

(q) $10,000 per year until 2025, grading off thereafter as described above.

291. Investment expenses, including fees for investment counsel, custody of assets, and other related items are not included in this section as they have already been implicitly recognized in our calculation of the valuation net discount rate (see Section 7.4).

292. The present values of the expenses are calculated as at the December 31, 2013 valuation date. For simplicity, we have assumed that the annual expenses thereafter are payable at the middle of each year, measured from December 31, 2013.

Item of expense	Present value at December 31, 2013 ($,000's)	
	Best Estimate	Sufficiency
Actuarial Financial Sufficiency	6,602	6,862
Actuarial Regular	1,424	1,483
Administration services	15,219	15,839
Arbitors/ Referees	294	305
Auditors	2,503	2,606
Class Member Communications	434	451
CBS	250	261
Independent Counsel	250	261
Monitor	924	956
Fund Counsel	1,386	1,434
Hema Quebec	75	78
Joint Committee Administration	10,915	11,333
Joint Committee Financial Sufficiency	5,693	5,902
Medical Modelling	1,909	1,984
Accounting Expert Testimony	409	425
Software development	250	261
Taxes (Federal GST/HST, Provincial QST)	4,918	5,111
Total	**53,455**	**55,552**

Appendix H – Payments and Amounts Specified in the Plan

293. As provided for in Section 7.02 of Schedule A - Transfused HCV Plan, the payment amounts and limits identified in Articles Four, Five and Six of the Plan are adjusted each year to reflect the increase in the CPI. The original 1999, and 2014, amounts are summarized below.

Section	1999 amount ($)	2014 amount ($)
4.01(1)(a)	10,000	13,457.74
(b)	20,000	26,915.48
(c)	30,000	40,373.22
(d)	65,000	87,475.30
(e)	100,000	134,577.39
4.02(2)(b)(i)[1]	2,300,000	3,095,279.91
4.03(2)	12	16.15
	240	322.99
4.04(a)	50,000	67,288.69
4.05	1,000	1,345.77
4.08	240,000	322,985.73
5.01(1)	5,000	6,728.87
	50,000	67,288.69
(2)	120,000	161,492.87
(3)	240,000	322,985.73
5.02(1)	5,000	6,728.87
(2)	240,000	322,985.73
6.01(2)	12	16.15
	240	322.99
6.02(a)	25,000	33,644.35
(b)	15,000	20,186.61
(c), (d), (e)	5,000	6,728.87
(f), (g)	500	672.89

[1] This amount was previously limited to $300,000 in 1999 dollars.

294. The Hemophiliac HCV Plan (i.e. Schedule B) provides for similar payments and amounts, with the following two additional items:

Section	1999 amount ($)	2014 amount ($)
4.08(2)	50,000	67,288.69
5.01(4)	72,000	96,895.72

Appendix I – Glossary of Abbreviations and Terminology

The following summarizes some of the abbreviations and terminology used in the report.

CASL: the Canadian Association for the Study of the Liver; developed the 1999 CASL report/study/model on the progression of hepatitis C, led by Dr. Murray Krahn; used by us in our 1999 actuarial assessment of the fund's assets and liabilities; published the special article *An update on the management of chronic hepatitis c: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver* which sets out current treatment protocols in Canada.

DA9: deaths after January 1, 1999

DB9: deaths before January 1, 1999 due to HCV related causes

Fibrosis Stages 0, 1, 2, 3, 4: indicating the disease development in the MMWG models, from infection (stage 0) through cirrhosis (stage 4); these stages do not correspond directly to the disease-based compensation Levels in the Plans

HCV: hepatitis C virus

Hemophiliac Plan: the Hemophiliac HCV Plan provided for in the Settlement Agreement

HIV Coinfection: the situation where a claimant is infected with both HCV and HIV. Additional benefits may be payable to coinfected claimants.

HIV Program: the HIV Secondarily Infected Program provided for in the Settlement Agreement

Known(s) or Known Claimant(s): those claimants who are known and approved before the actuarial assessment date

Level: a disease-based compensation level as defined under the Plans. Disease levels for the purpose of the Settlement Agreement do not correspond directly to the Fibrosis Stages, in the MMWG models.

MMWG: Medical Model Working Group; led by Dr. Krahn; convened to review and update the medical model for the 2001, 2004, 2007, 2010 and the 2013 assessments

Plans: Comprises the Hemophiliac and Transfused Plans

Previously Treated: refers to treatment with HCV treatment drugs prior to the actuarial assessment date.

Settlement Agreement: the agreement made as of June 15, 1999 between the governments and the counsel for the class action plaintiffs

SVC, short for Spontaneous Viral Clearance, refers to undetectable HCV viral load in serum, in the absence of treatment

SVR, short for Sustained Virological Response, refers to an undetectable HCV viral load test 12 weeks after completing a successful course of HCV treatment.

Transfused Plan: the Transfused HCV Plan provided for in the Settlement Agreement

Unknown(s) or Unknown Claimant(s): those claimants included in the actuarial assessment who are yet to be approved as claimants, and who are presumed to be approved after the actuarial assessment date. Unknowns consist of those who are known to the Administrator, but not yet approved as claimants, as well as those who have not yet lodged a claim

$50K+ option: for deaths before January 1, 1999, the option of choosing $50,000 plus claims by the family, including loss of support or loss of services

$120K option: for deaths before January 1, 1999, the option of choosing $120,000 in full settlement of all claims

Appendix J – Source Material

Document	Date	Author/Source
Copy of the data regarding the approved claimant cohort as at August 31, 2013, provided to the MMWG by the administrator, including claimant details such as disease state, drug therapy history, and results of claimant survey, including a question whether the claimant had cleared the virus	September 27, 2013 cover letter	Crawford Class Action Settlements
Copy of the data regarding the approved claimant cohort as at December 31, 2013, prepared at the request of the Joint Committee, including cohort details and payment history and a "worksheet references" document setting out field name definitions for claimant data	February 6, 2014 cover letter	Crawford Class Action Settlements
2013 MMWG report: Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus through the Blood Supply, 1986-1990 The Fifth Revision of Hepatitis C Prognostic Model Based on the Post-Transfusion Hepatitis C Compensation Claimant Cohort	September 2014	MMWG
2013 medical model in Tree-age software, corresponding to the 2013 MMWG report	September 2014	MMWG
Claim payment history updated to October 2014	November 2014	Crawford Class Action Settlements
Information on claims submitted under CAP 1 and CAP2	January 2015	Crawford Class Action Settlements
2013 Financial Sufficiency Review - Medical Evidence	February 13, 2015	Dr. Bain
An update on the management of chronic hepatitis C*: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver*	February 2015	CASL
Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System	February 2010	Chaudhary et al
Patient time costs and out-of-pocket costs in hepatitis C	November 2011	Dr. Krahn et al, Liver International
Annual reports for the HCV Trust from inception to 2013, including the audited financial statements	various	Joint Committee
Custodial statements for the Trust for 2011 through 2013 inclusive	various	RBC Investor Services
Copy of the original Settlement Agreement	June 1999	Joint Committee
Correspondence between Joint Committee and Eckler providing input from medical experts and the administrator regarding assumptions and the operations of the Trust	various	various
Correspondence between Morneau Shepell and Eckler regarding development of assumptions and methods	various	Morneau Shepell

Richard Border, FIA, FCIA,

Richard is a Principal and Shareholder based in the Vancouver office. He has over 25 years of actuarial experience in pension consulting, valuation of long-term liabilities (such as Workers' Compensation plans), investment consulting, technical design of investment and insurance products for pension plans, management information, and financial modeling.

Since joining Eckler in early 2002, Richard has specialized in pensions and workers compensation actuarial consulting. He is the lead actuary to public sector pension plans in British Columbia (specifically, the BC Public Service, Municipal, College, and Teachers' pension plans). His responsibilities for these clients include acting as lead consultant, providing technical actuarial analysis, as well as consulting advice and guidance on plan design issues. He is the external actuary for WorkSafeBC and is responsible for the actuarial opinion on the adequacy of the liabilities in the WorkSafeBC annual report. He has similar responsibilities for the Workers Compensation Board of Manitoba.

Richard has worked on the 2001, 2004, 2007 and 2010 HCV sufficiency reviews and has co-signed each of the associated reports.

Prior to joining Eckler, Richard's early career was with a large South African life insurer, both in South Africa and the UK. Subsequently he joined the investment consulting division of a large consulting firm before moving to Canada in 2001. He became a Canadian citizen in 2007.

Richard graduated from the University of Cape Town in 1986 with a BSc statistics. He is a Fellow of both the Institute and Faculty of Actuaries (UK) and the Canadian Institute of Actuaries.

This is Exhibit" B "referred to in the
affidavit of RICHARD BORDER
sworn before me at VANCOUVER
this 11 day of MARCH 20 15

A Commissioner for taking Affidavits
for British Columbia

Wendy Harrison

FSA, FCIA, is a Principal and Shareholder of Eckler based in the Vancouver office, with 14 years of experience as a consulting actuary with Eckler Ltd., and more than 28 years of actuarial experience, including the provision of actuarial services for pension plans; financial reporting and risk management for life insurers (including the valuation of long-term liabilities such as life and disability insurance and annuities); and Workers' Compensation plans. During her career, she has worked on a wide range of actuarial and business projects, such as mergers and acquisitions, determining appraisal values for financial institutions and valuing the liabilities related to class-action awards.

Wendy provides actuarial consulting services to a range of clients, including pension plans and financial institutions. She has primary responsibility for the WorkSafeBC defined benefit pension plan, as well as a number of other defined benefit pension plans ranging from university to multi-employer union plans. She is also the Appointed Actuary for Pacific Blue Cross, a B.C.-based provider of group life and health benefits.

Wendy has worked on and co-signed the 2004, 2007 and 2010 HCV sufficiency reports.

Before joining Eckler, Wendy was Vice President and Appointed Actuary for the Seaboard Life Insurance Company, based in Vancouver. As the Appointed Actuary for Seaboard, Wendy was responsible for the valuation of more than $1.5-billion in liabilities for insurance products sold throughout Canada and the United States, and for compliance with all relevant standards of practice and regulatory project requirements.

Wendy graduated from the University of Waterloo in 1985 with a joint honours degree in actuarial science and statistics. She is a Fellow of both the Society of Actuaries and the Canadian Institute of Actuaries, and is a Member of the American Academy of Actuaries.

This is Exhibit" C "referred to in the
affidavit of RICHARD BORDER
sworn before me at VANCOUVER
this 11 day of MARCH 2015

A Commissioner for taking Affidavits
for British Columbia

Dong Chen, FSA, FCIA

Dong is a consulting actuary who joined Eckler Ltd. in 2003, working part time while finishing his university studies. Since graduating from Simon Fraser University in 2004, he has been with Eckler on a full-time basis. Dong specializes in the valuation of private and public sector pension plans. He has worked on the 2004, 2007 and 2010 HCV fund sufficiency reviews.

He is a Fellow of both the Society of Actuaries and the Canadian Institute of Actuaries.

This is Exhibit" D "referred to in the
affidavit of RICHARD BORDER
sworn before me at VANCOUVER
this 11 day of MARCH 2015

A Commissioner for taking Affidavits
for British Columbia

Kevin Chen

Kevin Chen joined Eckler Ltd. in 2009 as a summer student, and then commenced permanent employment in January 2010. He has an undergraduate degree in actuarial science from Simon Fraser University, and completed a Master's degree in actuarial science from the University of Waterloo in 2010. He is making good progress with his Society of Actuaries exams and focuses on technical actuarial work, mainly in the pensions area. He has worked on the 2010 and 2013 HCV fund sufficiency reviews.

This is Exhibit" E "referred to in the
affidavit of RICHARD BORDER
sworn before me at VANCOUVER
this 11 day of MARCH 2015

A Commissioner for taking Affidavits
for British Columbia

C A N A D A
PROVINCE OF QUEBEC
DISTRICT OF MONTRÉAL

NO : 500-06-000016-960

S U P E R I O R C O U R T
Class Action

DOMINIQUE HONHON

Plaintiff

-vs-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Defendants

-and-

ME MICHEL SAVONITTO, ès qualités de membre du Comité conjoint

Petitioner

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A
PROVINCE OF QUEBEC
DISTRICT DE MONTRÉAL

NO : 500-06-000068-987

S U P E R I O R C O U R T
Class action

DAVID PAGE

Plaintiff

-vs-

PROCUREUR GÉNÉRAL DU CANADA
PROCUREUR GÉNÉRAL DU QUÉBEC
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE

Defendants

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

AFFIDAVIT

I, DR. VINCE BAIN, of University of Alberta, 1.55 Zeidler Center, 130 University Campus, Edmonton, Alberta, SWEAR (OR AFFIRM) THAT:

Qualifications

1. I am a physician specializing in gastroenterology and hepatology. I am a Fellow of the Royal College of Physicians of Canada in Internal Medicine and in Gastroenterology. I am a member of the College of Physicians and Surgeons in Alberta. I am Board certified by the American Board of Internal Medicine.

2. I have a clinical practice as well as teaching responsibilities at the University of Alberta. In my clinical practice, I treat persons who are infected with the Hepatitis C Virus ("HCV"). I estimate that I currently treat or follow 200 HCV patients. I estimate that I have treated more than 500 HCV patients over the course of my career.

3. I am a Professor in the Division of Gastroenterology, Department of Medicine at the University of Alberta I have had this position since 2002. I am also the Medical Director of the Liver Transplant Program at the University of Alberta and have been since 1989. Since 2000 I have been the Director of the Liver Unit, Division of Gastroenterology, Department of Medicine, at the University of Alberta.

4. From 2000-2002 I was the Chairman of the Hepatology and Liver Transplant Committee of the Canadian Association of Gastroenterology. I am a member of the Canadian Association for the Study of the Liver, known as CASL, a society consisting of Canadian gastroenterologists and hepatologists (gastroenterologists who specialize in the treatment of the liver). From 2002-2004 I was the President of CASL. From 2004-2006 I was the Chairman of the Medical Advisory Board of the Canadian Liver Foundation.

5. A copy of my curriculum vitae is attached as **Exhibit "A"** to this affidavit.

6. This affidavit addresses the nature of HCV, its disease stages, co-morbidities, treatment, and outcomes. I have reviewed the affidavits of Dr. Frank Anderson sworn in this matter. This affidavit updates the information provided in those affidavits,

particularly in the area pertaining to treatment and treatment outcomes. The sections of this affidavit headed the Hepatitis C Virus and Course of Infection include summaries of the more detailed information provided in Dr. Anderson's previous affidavits to provide the reader with context to understand the updates on treatment and outcomes. Those previous sections are summarized (as opposed to composed anew) as I agree with them and saw no need to rewrite them.

7. In making this affidavit, I certify that I am aware that my duty is to:

(a) provide opinion evidence that is fair, objective and non-partisan and related only to matters within my area of expertise; and

(b) assist the court and provide such additional assistance as the court may reasonably require to determine a matter in issue.

8. I am aware that the foregoing duties prevail over any obligation I may owe to any party on whose behalf I am engaged and I am aware that I am not to be an advocate for any party. I confirm that this affidavit conforms with the above-noted duties. I further confirm that if called upon to give oral or written testimony, I will give such testimony in conformity with these duties.

The Hepatitis C Virus

9. Hepatitis means inflammation of the liver. Inflammation causes damage to liver cells and death of liver cells. Ongoing inflammation leads to fibrosis which is progressive. The virus causing Hepatitis C was identified in late 1989 and the first diagnostic serum tests appeared in 1990.

Nature of the Virus and Genotypes

10. HCV is a ribonucleic ("RNA") virus. The virus takes the form of six different "genotypes" which vary in distribution worldwide. These genotypes are described with numbers 1 to 6. There are smaller differences within each genotype referred to as "subtypes", and these are designated a, b and c. The process of determining the

genotype and subtype with which a person is infected is called genotyping and subtyping.

11. Some patients may have a more virulent clinical course, and certain genotypes respond less well to a given treatment than others. The virus may mutate during viral replication and possibly as a result of treatment. This is common in RNA viruses because their method of replication involves many spontaneous errors. Mutation, particularly during treatment, may cause the virus to become resistant to treatment.

12. It is standard to conduct a genotype assessment of all persons undergoing treatment and to tailor the treatment based on the genotype.

13. The various genotypes in Canada are as follows:

(a) genotype 1 accounts for approximately 65% of Canadians infected with HCV (this number varies from province to province);

(b) genotype 2 accounts for approximately 14% of Canadians infected with HCV;

(c) genotype 3 accounts for approximately 20% of Canadians infected with HCV; and

(d) a very small proportion of Canadians infected with HCV are infected with genotypes 4, 5 and 6 (less than 1 %).

Blood Tests for Diagnosis

14. Blood tests are used to determine whether a person is or was infected with HCV. The presence of the antibody to HCV in the blood of a person reveals whether or not the person has ever been infected with HCV. It does not determine whether the person is currently infected with HCV or when the person became infected with HCV. A polymerase chain reaction ("PCR") test reveals whether detectable levels of RNA of the virus are present in the blood of a person, and as such determines whether a person is currently infected with HCV.

Course of Infection

Acute HCV

15. Once infected with HCV, a person will either clear HCV after an acute stage of the illness within approximately six months of infection, or the person will develop chronic HCV infection. The medical literature establishes that approximately 25% of all persons infected clear HCV within approximately one year of infection. Those persons will still test positive for the antibody but will not test positive on a PCR test, nor will they experience any progressive liver disease due to HCV.

Chronic HCV – Inflammation and Fibrosis

16. Persons who do not clear the virus after the acute stage of the illness have chronic HCV. The extent to which they experience progressive liver disease depends on the virulence of their particular virus and host factors such as their age, their alcohol intake and whether treatment achieves a sustained viral response which is synonymous with cure (described below).

17. HCV causes inflammation, scarring (fibrosis) and death (necrosis) of liver cells.

18. The level of inflammation varies among HCV patients. The various levels of inflammation are referred to as grades and the grading system is from 0 to 4 in the Metavir system. Zero inflammation means no inflammatory cells, and grade 4 inflammation means severe inflammation throughout the whole of the liver lobule. The higher the grade of inflammation, the more inflammatory activity is present. The inflammation may vary in intensity from time to time, at times being much more severe than other times.

19. Inflammation and necrosis of liver cells results in scarring of liver tissue (fibrosis). Fibrosis also appears in various patterns in HCV patients, and these patterns are referred to as stages. The higher the stage, the more marked the pattern of fibrosis in the liver.

20. Fibrosis generally increases over time. Research has been done on the development of fibrosis, and indicates that the process of fibrosis and scar formation is

fairly lengthy. There is a stage at which fibrosis is "immature" i.e. the scar formation has not condensed, and such immature fibrosis may improve with sustained viral response after therapy.

21. The stages of fibrosis are based on the predictable pattern of scarring which hepatitis causes in the liver. The liver consists of anatomic units referred to as liver lobules. Each liver lobule has a central vein and portal triads which are joined by lines or tracks of liver cells. Blood enters the liver through arteries and veins in the portal triads, flushes along the liver cells, and leaves through the central vein.

22. In chronic viral hepatitis the inflammation is more prevalent in and around the portal triads. The cells around the portal triads may be destroyed (cell necrosis), a process referred to as interface hepatitis. The inflammation progresses beyond the portal triads along the liver tracks to reach the central veins. Fibrosis confined to the portal areas or with short extensions is referred to as non-bridging fibrosis (F1 or F2). When the pattern of fibrosis begins to extend from a portal triad to a central vein, or between portal triads, the fibrosis is referred to as bridging (F3). Bridging between all the veins and all the triads and between all the triads in a lobule is called cirrhosis. This pattern is characterized by complete circles of scar or fibrosis as viewed in two dimensions as we see on liver biopsies (or spheres in 3D) and this causes the typical nodular pattern of a cirrhotic liver (F4).

23. The most commonly utilized method (Metavir) of staging fibrosis utilizes the following four stages:

(a) F0 – no fibrosis (disease levels 1 and 2 in the Settlement Agreement and Plans);

(b) F1 – minimal fibrotic changes which do not extend beyond the portal areas (included in disease level 3 in the Settlement Agreement Plans);

(c) -F2 – fibrotic changes to portal areas with short extensions (included in Disease Level 3 in the Settlement Agreement Plans);

(d) F3 – fibrotic changes to the liver known as bridging fibrosis (corresponds to Disease Level 4 the Settlement Agreement Plans); and

(e) F4 – cirrhosis – fibrotic changes which have become cirrhotic (corresponds to Disease Level 5 in the Settlement Agreement Plans).

24. Many patients are asymptomatic prior to developing cirrhosis or HCC.

25. Pre-cirrhotic symptoms, for those who experience them, include: fatigue, weight loss, upper right abdominal discomfort, mood disturbance, poor concentration, anxiety and depression. Of those symptoms, fatigue is the most common. Patients typically describe the fatigue as a feeling of exhaustion and lack of energy.

Cirrhosis and End Stage Liver Disease

26. Once a patient is cirrhotic, they are either a compensated cirrhotic, or a decompensated cirrhotic, depending on their liver function. Where there are enough viable liver cells to maintain liver function, notwithstanding the cirrhotic pattern, the person has compensated cirrhosis.

27. Decompensated cirrhosis occurs when the liver is no longer able to perform one or more of its essential functions. It is caused by loss of liver cells, but more importantly, by progressive fibrosis that interferes with normal blood flow through the liver. It is diagnosed by the presence of one or more conditions which alone or in combination is life threatening without a transplant. This is also referred to as liver failure or end stage liver disease.

28. With decompensated cirrhosis critical liver functions are impaired and the condition is referred to as liver failure. Life is threatened. Conditions which define liver failure include gastrointestinal haemorrhaging, ascites (fluid build up in the abdomen), inadequate excretion of bilirubin by the liver causing jaundice or failure to remove the usual toxins absorbed from the bowel (which in turn can affect brain cells causing drowsiness, confusion and possibly coma, known as hepatic encephalopathy). These severely ill patients also experience protein malnutrition causing bruising, bleeding and

muscle wasting. Other organ failure may occur with progressive disease most commonly involving the lungs and kidneys.

29. Patients who progress to cirrhosis with or without decompensation may develop hepatocellular cancer ("HCC"). This is a primary form of liver cancer secondary to viral infection or cirrhosis. HCC is included in Level 6 in the Settlement Agreement Plans.

Co-Morbidities

30. Some patients with HCV suffer from conditions which are related to their infection with HCV; others to which they are more vulnerable to developing as a result of infection with HCV; or others for which HCV exacerbates the condition. Some of these are conditions which also occur in patients who do not have HCV. Such conditions are considered co-morbidities and they include:

(a) HCC - discussed above;

(b) pain – in general liver disease is not painful but some patients experience upper right quadrant pain and HCV-associated fatigue can exacerbate other medical conditions which have pain;

(c) mental illnesses such as depression and anxiety – HCV patients, some of whom have a history of intravenous drug use ("IVDU"), often have mental illnesses. HCV patients who have no history of IVDU also can experience mental illness but it is less frequent. It is understood that HCV affects the brain in some ways, and some patients describe "brain fog" and have difficulty concentrating. Other HCV patients have a reactive depression, ie: reactive to liver disease with a chronic course and a potentially life-threatening outcome;

(d) diabetes – the incidence of diabetes is higher in the HCV population than the general population;

(e) mixed cryoglobulinemia – this refers to the production of abnormal proteins referred to as globulins. These proteins may form aggregates

that can adversely effect small blood vessels sometimes causing inflammation in these vessels referred to as "vasculitis". Treatment of the HCV will reduce the severity of this condition but not completely cure it;

(f) erythema multiform, erythema nodosum, lichen planus and others - skin conditions that manifest as a rash over parts of the body or red raised bumps over the shins and lower legs;

(g) glomerulonephritis – inflammation in the kidneys due to vasculitis which results in protein and blood cells in the urine and in some instances results in kidney failure. Treatment of HCV, if successful, will reduce the severity of this disease and avoid kidney failure unless the patient has already progressed to kidney failure;

(h) thyroid diseases – both overactive (hyperthyroidism) and underactive (hypothyroid) thyroid disease may occur;

(i) polyarteritis – inflammation of small blood vessels with skin rash, arthritis and sometimes swelling of the legs;

(j) porphyria cutanea tarda – a condition characterized by painful blisters on the exposed skin areas, particularly the hands and face. The blisters break leaving open sores, which eventually heal but often leave a scar;

(k) thrombocytopenia – low platelets resulting in increased bruising and bleeding;

(l) uveitis, Mooren corneal ulcers – inflammation of the eye or ulcers of the cornea of the eye. These conditions may be serious and threaten eyesight;

(m) Sjogren's syndrome – lack of production of tears and saliva; and

(n) B-cell lymphoma – this is a cancer of the lymph glands, although the increased frequency in HCV is still debated.

Treatment

Antiviral Therapy

31. The Canadian Association for the Study of the Liver ("CASL") produces guidelines for the management of HCV every few years.

32. The most recent guidelines are the 2015 Consensus Guidelines from the Canadian Association for the Study of the Liver. They were published in the Canadian Journal of Gastroenterology and Hepatology, Can J Gastroenterol Hepatol Vol 29 No 1 January/February 2015. They are attached as **Exhibit "B"** to this affidavit. The CASL guidelines are recommendations rather than strict standards.

33. The goal of antiviral therapy is complete eradication of the virus from the patient, thereby stopping the inflammation and preventing further scarring and death of liver cells. Reversal of fibrosis is possible in some patients. In others with advanced cirrhosis the extent of scarring is so great that the liver may proceed to liver failure notwithstanding the cessation of inflammation. The precise threshold for recovery is not well understood and even in those patients who progress, eradication of the virus is still beneficial because if a liver transplant can be performed, the new liver will not be re-infected.

34. Eradication of the virus is determined by measuring the amount of virus in the blood on PCR testing. If the virus drops below detectable levels, and stays below detectable levels for 12 weeks after antiviral treatment, a sustained viral response ("SVR") has been achieved. This additional 12 weeks of observation is a surrogate way to show that the entire body and not just the blood compartment has been cleared of virus. If virus remains, for example in the liver or lymph nodes, despite the blood being clear at the end of treatment, it will begin to replicate and reappear in blood within 12 weeks.

35. The major forms of antiviral therapy in the history of treating hepatitis C have been as follows:

(a) interferon monotherapy which consisted of injections of interferon;

(b) combination interferon and ribavirin therapy, which progressed to delivery of the interferon in a long-acting, pegylated form, still injected, and ribavirin pills, known as pegylated interferon and ribavirin combination therapy; and

(c) direct-acting anti-viral agents, some of which were initially added to pegylated interferon and ribavirin combination therapy. Others are given without either interferon or ribavirin, some are given with one or the other of pegylated interferon or ribavirin, depending on the circumstances of the patient.

36. Both interferon and ribavirin can cause significant side effects. The number and adverse nature of the side effects are more pronounced with interferon. In addition, these drugs are contra-indicated for people with other medical conditions, co-morbidities or who are taking certain other drugs. Accordingly, there has been extensive research into direct-acting antiviral agents which are effective without interferon and/or ribavirin. Currently, antiviral therapy with direct-acting agents and without the use of interferon and/or ribavirin is possible for most persons infected with HCV, as described below.

37. The first generation of direct-acting antiviral agents were protease inhibitors called telaprevir and boceprevir and they were approved for treatment in 2011. They were prescribed with pegylated interferon and ribavirin. Although they had increased SVR rates compared to interferon and ribavirin alone, they also had severe side effects and many associated drug interactions. Telaprevir and boceprevir are rarely prescribed in Canada anymore.

38. The next direct-acting antiviral agent approved for use in Canada was simeprevir, which was also prescribed with pegylated interferon and ribavirin in genotype 1 patients. It was approved in 2013. Its use is now limited in favour of interferon-free combinations.

39. Also in 2013, sofosbuvir was approved for use with pegylated interferon and ribavirin for genotypes 1 and with ribavirin only for genotypes 2 and 3. Its use has also now changed, as described below.

40. In late 2014 and early 2015, treatments that exclude pegylated interferon and ribavirin were approved and they are the treatments that are and will be most commonly prescribed. They are:

(a) a combination of sofosbuvir and ledipasvir which was developed by Gilead and is marketed as Harvoni in Canada; and

(b) a combination of ombitsavir; dasabuvir; paritaprevir which is known in the HCV medical treating community as "3D" (for three direct-acting antiviral agents). This was developed by AbbVie, and is marked as the Holkira Pak. This combination also includes ritonavir as a "boost" in order to enhance the anti-viral effect by reducing metabolism of one of the active drugs. In some patients ribavirin will be necessary.

41. With a few exceptions described below, each of these advancements is effective in persons not previously treated; is effective in those treated previously who did not respond; has been associated with increased sustained viral responses among certain genotypes; has a shorter treatment duration, is available to an increased number of patients (fewer contraindications or incompatibilities); and is associated with increased chances of tolerating the treatment and being able to finish the course of treatment. In sum, the efficacy of treatment has increased from about 5-10% (interferon monotherapy) to 95-99% (direct-acting anti-viral agents), while decreasing the duration of treatment and increasing the number of persons who can be treated and complete treatment. Treatment challenges for certain categories of patients remain, such as genotype 3 patients with cirrhosis. In this group SVRs of about 80% can be achieved and improvements are expected.

42. The cost of treatment has also gone up. The range is about $50,000 for 8 weeks to $76,000 for 12 weeks. If ribavirin is added, the additional cost is approximately $3,800-$4,400 for 12 weeks.

Treatment Duration

43. Treatment duration is important for several reasons. Generally, the shorter the treatment the more likely it is that the drugs will be taken in the correct amount at the correct time, which increases the likelihood of a sustained viral response. In addition, if the drugs cause side effects or medical complications, the shorter the treatment the more likely it is that the patient can endure the treatment.

44. Treatment duration also affects affordability of the treatment. Some private health care plans and this Settlement Agreement cover the newest drugs. Provincial drug coverage plans consider new drugs as they are approved by Health Canada, but coverage, if it is provided, lags behind approval.

45. Under the older treatment regimes, treatment duration was response guided. Response guided therapy involves testing viral load at certain times during treatment and either discontinuing (because viral load has not decreased significantly) or continuing therapy.

46. With the current treatments of direct-acting anti viral agents, the CASL guidelines recommend treatment duration which is set at the outset and which depends on genotype, clinical stage of disease, whether the person has been previously treated and drug combination. These recommendations demonstrate variability in treatment length from 8 weeks to 24 weeks. The majority of patients will receive 12 weeks of treatment with either Harvoni or Holkira Pak. The following are the exceptions:

(a) genotype 1 patients who are not cirrhotic, have never been treated and who have a low viral count may be treated for 8 weeks with Harvoni;

(b) genotype 1 patients who are cirrhotic and who have failed treatment previously, will be treated with Harvoni for 24 weeks unless ribavirin is added, in which case they will be treated with Harvoni and ribavirin for 12 weeks. Ribavirin is less expensive than Harvoni so some will likely opt for a 12 week course of Harvoni and ribavirin in this patient subgroup;

(c) genotype 1a patients who have cirrhosis and who were treated previously but did not respond may be treated with the Holkira Pak for 24 weeks;

(d) genotype 2 patients who are cirrhotic will be treated for 12 weeks with pegylated interferon, sofosbuvir and ribavirin or with sofosbuvir and ribavirin for 16 weeks;

(e) genotype 3 patients. The treatment of genotype 3 patients is set out in Table 7 of the CASL guidelines. There are many options depending on the status of the patients. In summary, they will be treated for either 12 or 24 weeks and some will be treated with a combination of drugs including interferon and/or ribavirin if they can tolerate it.

Treatment of Persons Who Are Co-Infected with HIV

47. The guidelines for treatment of persons who are co-infected with HIV are published by the Canadian Institute of Health Research HIV Trials. The current guidelines, published in October 2014, are attached as **Exhibit "C"** to this affidavit.

48. The SVR rate in HIV co-infected persons under the treatments in use at this time, as described above, are very similar to those who are mono-infected. All HIV co-infected patients should be considered for treatment.

49. The guidelines were published before specific studies for HIV co-infection had been published on Harvoni or Holkira Pak and so those drugs are not included in the recommendations. In my view, Harvoni and Holkira Pak have surpassed the guidelines and will be the primary types of treatment for HIV co-infected persons.

Side Effects

50. Interferon and ribavirin both cause severe side effects that made the therapies contraindicated in patients with certain other health issues; that interfered with completion of the therapy due to complications which arose from the side effects; and that caused significant morbidity in many patients while on the therapy. The first

approved direct acting anti-viral agents, telaprevir and boceprevir, also had significant side effects that were severe in some patients.

51. Because Harvoni and Holkira Pak are effective in some patients without interferon or ribavirin, the side effects and contraindications of these new combinations are markedly diminished. These drugs cause side effects in some patients but they tend to be less severe, do not create contraindications for treatment and they are not expected to imperil the chances of the patient completing the treatment. The side effects noted in the studies leading up to their approval are:

(a) patients taking Harvoni experienced mild to moderate fatigue, headache, insomnia and nausea; and

(b) patients taking Holkira Pak experienced fatigue, headache, nausea, pruritus (itchiness), insomnia, diarrhea and asthenia (lack of energy).

Health Outcomes After A Sustained Viral Response

52. Many factors, including medical, psychological, age, and socio-economic, will play a role in determining whether a person returns to baseline health status after attaining an SVR. It must be remembered that many of the persons were infected with the disease for 10-30 years before being cured. The comparison of good health at the time they were infected to the time they were cured is not straightforward.

53. Persons who were not disabled from HCV prior to treatment and who obtain an SVR during treatment will not go on to develop disabling symptoms materially contributed to be HCV with these exceptions:

(a) as discussed above, achieving an SVR significantly reduces the risk of HCC but it is not reduced to zero. Persons who had HCV and attained an SVR still have a higher risk of HCC than the general population. HCC occurrence post-SVR would be considered to be materially contributed to by previous infection with HCV;

(b) persons who have been successfully treated and who are asymptomatic after treatment may have future symptoms if they have an additional liver insult such as infection with another hepatitis virus, an autoimmune disease or alcoholism. Their past infection with HCV would be considered to materially contribute to renewed symptoms after liver insult unless they had no scarring of the liver at the time of their cure; and

(c) persons who had advanced cirrhosis may have crossed a threshold whereby the damage to the liver is so profound that the liver will continue to progress towards decompensation.

54. Many persons who were pre-cirrhotic when treated but were disabled from working or performing household duties and services will recover post-SVR and be able to return to work and household duties within a year of cessation of treatment.

55. Fewer, but a still significant number of patients who have compensated cirrhosis when treated and who were disabled at the commencement of treatment return to work or household duties after SVR and do so within one year of the cessation of treatment. Patients with decompensated cirrhosis are rarely working when treatment commences. Generally, their ability to return to work will depend on whether they receive a liver transplant after achieving an SVR. If they do, many will return to work within a year of the liver transplant. In the absence of a liver transplant, those who have liver failure will not return to work even though an SVR is achieved.

56. Those who are not able to return to work or household duties are impacted by factors such as:

(a) continuation of the most common symptom of HCV – debilitating fatigue – which does not always improve post-SVR;

(b) co-morbidities which may be materially contributed to by their infection with HCV or may have no causal connection to infection with HCV;

(c) age;

(d) motivation which can be affected by the nature of the work or the ease of return to work; and

(e) the longer patients have been off work, the less likely they are to return.

57. After SVR, prior infection with HCV can be a material contributor to death in those who:

(a) had liver failure at the time SVR is achieved and liver transplant does not occur or is not successful;

(b) have a subsequent insult to the liver such as another hepatitis infection, an autoimmune disease, or alcoholism; or

(c) develop HCC.

Post-SVR Treatment and Monitoring

58. Persons who have cirrhosis prior to attaining an SVR require screening for HCC every six months. They may also need gastroscopies to screen for esophageal varices. They should be followed by a hepatologist, gastroenterologist or internal medicine specialist.

59. Persons who did not have cirrhosis do not usually need to continue to see a specialist but instead are treated by their family doctors. On follow up, if the liver function tests show an increase in their ALT, they should have a repeat HCV RNA test. Literature suggests recurrence of HCV in patients who achieve an SVR to be less than 2%.

Liver Transplants

60. Transplantation does not cure the infection, but restores healthy liver function. However, post-transplant, the rate of liver damage (fibrosis) is accelerated so that about 30% of patients, in the absence of treatment, will be cirrhotic by 5 years. Patients with recurrent HCV have a reduced lifespan over and above the reduced lifespan seen in liver transplant patients.

HCC

61. Treatment options for HCC include resection of the tumour, alcohol injection into the tumour, embolization of the blood supply to the tumour along with the injection of anticancer drugs or radioactive beads, and radiofrequency ablation of the tumour. Transplantation may be considered for selected tumours before there is much likelihood of metastasis (spread of the tumour outside of the liver).

SWORN (OR AFFIRMED) BEFORE ME)
at Edmonton, Alberta, on)
11 /Mar/2015.)
)
)
)
)
)
A Notary Public or a Commissioner of)
Oaths in Alberta)

Yolanda Van Wachem
Barrister & Solicitor

DR. VINCE BAIN

This is Exhibit "A" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta
this 11 day of MARCH, 2015.

A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor



November 3, 2014

BIRTHPLACE:	Edmonton, Alberta, Canada
CITIZENSHIP:	Canadian
DOB:	October 12, 1957
MARITAL STATUS:	Married - Lola T. Baydala (MD, FRCPC - Pediatrics) 3 Children (Graham, Jessie, Tamara)
EDUCATION:	1975 - Senior Matric (Honors) - Strathcona Composite High School, Edmonton. 1979 - B.Sc. with Distinction, University of Alberta, Edmonton, Canada. 1981 - M.D. First-Class Standing with Distinction, University of Alberta, Edmonton, Canada.
INTERNSHIP:	1981 - 1982 - Rotating Intern, Victoria Hospital, London, Ontario.
RESIDENCY:	1982 - 1985 - Resident in Internal Medicine, University of Alberta Hospital, Edmonton, Alberta. Director: Dr. A.M. Edwards.
FELLOWSHIPS:	1985 - 1987 - Gastroenterology, University of Alberta Hospital, Edmonton, Alberta. Director: Dr. A.B.R. Thomson. 1987 - 1989 - MRC Research Fellow, Liver Unit, Kings College Hospital, London, England. Supervisor: Dr. Roger Williams.
CURRENT POSITIONS:	Professor, Div of Gastroenterology, Dept of Medicine, University of Alberta, Edmonton, Canada, 2002 - present.

Medical Director, Liver Transplant Program,
University of Alberta, Edmonton, Canada, 1989-Present.

Director, Liver Unit, Div of Gastroenterology
Department of Medicine, University of Alberta
Edmonton, Canada, 2000 - Present

PREVIOUS POSITIONS:

Associate Professor, Div of Gastroenterology,
Dept of Medicine, University of Alberta,
Edmonton, Canada, 1995 - 2002

Assistant Professor, Division of Gastroenterology,
Department of Medicine, University of Alberta,
Edmonton, Canada, 1989 - 1994.

Program Director, GI Fellowship Program,
University of Alberta, Edmonton, Canada, 1992 - 1997.

NATIONAL ADMIN POSITIONS:

1998-2000	-Chairman, Education Comm, Cdn Assoc. for the Study of the Liver.
2000-2001	-Vice President, Cdn Assoc. for the Study of the Liver.
2000-2002	-Chairman, Hepatology and Liver Transplant Committee, Cdn Assoc. of Gastroenterology.
2002-2004	-Vice-Chair, Medical Advisory Board, Canadian Liver Foundation
2002-2004	-President, Cdn Assoc for the Study of the Liver.
2004 - 2006	-Chairman, Medical Advisory Board, Canadian Liver Foundation

PROFESSIONAL QUALIFICATIONS:

1981	- Licentiate, Medical Council of Canada.
1982	- National Board of Medical Examiners.
1985	- American Board of Internal Medicine.
1986	- Fellow of the Royal College of

		Physicians of Canada - Internal Medicine.
	1987	- Fellow of the Royal College of Physicians of Canada - Gastroenterology.
	1990	- Fellow, American College of Physicians.
LICENCES:	1983- Present	- College of Physicians and Surgeons of Alberta.

PROFESSIONAL SOCIETIES AND ORGANIZATIONS:

Alberta Medical Association.

American Association for the Study of Liver Disease.

Canadian Association of Gastroenterology.

Canadian Association for the Study of Liver Diseases.

Canadian Medical Association.

Canadian Transplant Society

European Association for the Study of Liver Diseases.

AWARDS

Jonathon B Meddings Clinical Innovation Award 2009-2010

Distinguished Service and Meritorious Achievement Award, Canadian Assoc for the Study of the Liver 2012

Excellence in Humanism Certificate, Presented by the Faculty of Medicine and Dentistry, 2013.

Awarded Fellowship Designation in the American Association For the Study of Liver Diseases, 2014.

JOURNAL AND GRANT REVIEWS:
(last 5 years)

2002 - 2012 - American Journal of Transplantation-Reviewer

2014 – Liver Transplantation – Reviewer

2014 – World Journal of Gastro - Reviewer

1990 - 2012 - Canadian Journal of Gastroenterology. **2000 - 2003**, Editorial Board

2009 - 2012 – Transplantation

2012 – Journal of Viral Hepatitis

2010 -2014– Hepatology – Reviewer

PUBLICATIONS:

A. Peer Reviewed Articles

1. Bain GO and **Bain VG**.
   Increased numbers of lymphocytes with single class surface immunoglobulins in Hodgkin's Disease.
   American Journal of Clinical Pathology 82:674, 1984.

2. **Bain VG** and Bain GO.
   Lymphocyte populations with abnormal Kappa: Lambda ratios in reactive lymphoid hyperplasia.
   Journal of Surgical Oncology 29:227, 1985.

3. **Bain VG**, Ardao GH, Kowalewska-Grochowska K, Wensel RH and Jewell LD.
   Biliary Ascariasis.
   Journal of Clinical Gastroenterology 10:448, 1988.

4. **Bain VG** and Alexander GJM.
   Progress in the treatment of chronic hepatitis B.
   Journal of Antimicrobial Chemotherapy 22:780, 1988.

5. **Bain VG**, Daniels HM, Chanas A, Alexander GJM, Williams R.
   Foscarnet therapy in chronic hepatitis B virus E antigen carriers.
   Journal of Medical Virology 29:152, 1989.

6. **Bain VG**, Bailey RJ, Jhamandas JH.
   Post-shunt myelopathy.
   Journal of Clinical Gastroenterology 13:562, 1991.

7. Lau JYN, Hansen LJ, **Bain VG**, Chaggar K, Smith HM, Portmann BC, Vergani D, Alexander GJM, Williams R.

Expression of intrahepatic hepatitis D viral antigen in chronic HDV infection.
Journal of Clinical Pathology 44:549, 1991.

8. Lau JYN, **Bain VG**, Davis SE, Alexander GJM, Williams R.
Export of intracellular hepatitis B virus (HBV) surface antigen in chronic HBV infection is related to viral replication.
Hepatology 14:416, 1991.

9. Lau JYN **Bain VG**, Naoumov NV, Smith HM, Alexander GJ Williams R.
Effect of gamma interferon on hepatitis B viral antigen expression in primary hepatocyte culture.
Hepatology 14:975,1991.

10. Fingerote RJ, **Bain VG**, Fedorak RN.
Liver transplants for alcoholic liver disease.
Canadian Journal of Gastroenterology 5:195,1991.

11. Lau JYN, **Bain VG**, Smith HM, Alexander GJ, Williams R.
Modulation of hepatitis B viral antigen expression by immunosuppressive drugs in primary hepatocyte culture.
Transplantation 53:894, 1992.

12. Lau JYN **Bain VG**, Davies SE, O'Grady JG, Alberti A, Alexander GJM, Williams R.
High level expression of hepatitis B virus antigens in fibrosing cholestatic hepatitis.
Gastroenterology 102:956,1992.

13. Fingerote RJ, **Bain VG**.
Fulminant hepatic failure.
American Journal of Gastroenterology 88:1000, 1993.

14. Mason AL, Wick M, White HM, Benner KH, Lee RG, Regenstein F, **Bain VG**, Campbell C, Perrillo RP.
Increased hepatocyte expression of hepatitis B virus transcription in patients with features of fibrosing cholestatic hepatitis.
Gastroenterology 105:237, 1993.

15. Duerksen DR, Jewell LD, **Bain VG**.
Hepatic giant cell arteritis and polymyalgia rheumatica.
Canadian Journal of Gastroenterology 8:36, 1994.

16. Ma M, Ryan E, **Bain VG**.
The development of hemochromatosis after treatment for celiac sprue.
Canadian Journal of Gastroenterology 8:358, 1994.

17. Tipples GA, Ma MM, Fischer KP, **Bain VG**, Kneteman NM, Tyrrell DL.
Mutation in HBV RNA-dependant DNA polymerase confers resistance to lamivudine in vivo.

Hepatology 24:714, 1996.

18. Shapiro AMJ, **Bain VG**, Sigalet DL, Kneteman NM.
Rapid resolution of chylous ascites after liver transplantation using somatostatin analog and total.
Transplantation 61:1410, 1996.

19. **Bain VG**, Kneteman NM, Ma MM, Gutfreund K, Shapiro AMJ, Fischer KP, Tipples G, Lee H, Jewell LD, Tyrrell DL.
Efficacy of lamivudine in chronic hepatitis B patients with active viral replication and decompensated cirrhosis undergoing liver transplantation.
Transplantation 62:1456,1996.

20. Duerksen DR, Jewell LD, Mason AL, **Bain VG**.
Co-existence of hepatitis A and adult Reye=s syndrome.
GUT 41:121, 1997.

21. Yoshida EM, Ma MM, Davis JE, Fischer KP, Kneteman NM, Erb SR, Tyrrell LD, **Bain VG**.
Post-liver transplant allograft re-infection with a lamivudine resistant strain of hepatitis B virus: long term follow-up.
Canadian Journal of Gastroenterology 12:125, 1998.

22. Kassam N, **Bain VG.**
Liver transplantation for neuropsychiatric Wilson disease.
Canadian Journal of Gastroenterology 12:65, 1998.

23. Poynard T, Marcellin P, Lee S, Niederau C, Minuk G, Ideo G, **Bain VG**, Heathcote J, Zeuzem S, Trepo C, Albrecht J.
An international randomized trial of interferon alfa-2B and ribavirin 48 or 24 weeks vs interferon alfa-2B 48 weeks, for first line treatment of chronic hepatitis C.
Lancet 352:1426, 1998.

24. Everson GT, Jensen DM, Craig JR, van Leeuwen DJ, **Bain VG**, Ehrinpreis MN, Albert D, John T, Witt K, and the Consensus Interferon Study Group.
Efficacy of interferon treatment for patients with chronic hepatitis C: comparison of response in cirrhotics, fibrotics or nonfibrotics.
Hepatology 30:271, 1999.

25. Wong W, **Bain VG**.
Update in liver transplantation.
Canadian Family Physician 45:1241, 1999.

26. Pockros PJ, **Bain VG**, Hunter EB, Conrad A, Balart LA, Hollinger FB,Albert D, and the Consensus Interferon Study Group.
A comparison of RT-PCR and bDNA assays for hepatitis C virus in patients receiving interferon treatment.

Journal of Viral Hepatitis 6:145, 1999.

27. Shapiro AMJ, **Bain VG**, Preiksaitis JK, Ma MM, Issa S, Kneteman NM.
Oglivie=s syndrome associated with acute cytomegaloviral infection after liver transplantation.
Transplant International 13:41,2000.

28. Gutfreund KS, **Bain VG.**
Chronic viral hepatitis C: Management update.
Canadian Medical Association Journal 162:827, 2000.

29. **Bain VG**, Abraham N, Jhangri GS, Alexander TW, Henning RC, Hoskinson ME, Maguire CG, Lalor EAG, Sadowski DC.
Prospective study of biliary strictures to determine the predictors of malignancy.
Canadian Journal of Gastroenterology 14:397, 2000.

30. Gutfreund KS, Williams M, George R, **Bain VG**, Ma MM, Yoshida EM Villeneuve J-P, Fischer KP, Tyrrell DLJ.
Genotypic succession of mutations of the hepatitis B virus polymerase associated with lamivudine resistance.
Journal of Hepatology 33:469, 2000.

31. Romagnuolo J, Jewell DL, Kneteman NM, **Bain VG**.
Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis.
Canadian Journal of Gastroenterology 14:637, 2000.

32. **Bain VG.**
Hepatitis B in transplantation.
Transplant Infectious Disease 2:153, 2000.

33. **Bain VG**, Montero J-L, de la Mata M.
Bioartificial liver support.
Canadian Journal of Gastroenterology 15:313, 2001.

34. Romagnuolo J, Jhangri GS, Jewell LD, **Bain VG**.
Predicting the liver histology in chronic hepatitis C: How good is the clinician?
American Journal of Gastroenterology 96:3165, 2001.

35. Wong P, Houston S, Power B, Lalor E, **Bain VG**.
A case of histoplasma capsulatum causing granulomatous liver disease and Addisonian crisis.
Canadian Journal of Gastroenterology 15:687, 2001.

36. **Bain VG**.
Effect of HCV viral dynamics on treatment design: lessons learned from HIV.
American Journal of Gastroenterology 96:2818, 2001.

37. Ramji A, Yoshida EM, **Bain VG** et al.
Late Acute Rejection After Liver Transplantation: The Western Canada Experience.
Liver Transplantation 8:945-951, 2002.

38. **Bain VG**, Wong WW, Greig PD and Yoshida EM.
Hepatology and the Canadian Gastroenterologist: Interest, Attitudes and Patterns of Practice. A National Survey from the Canadian Association of Gastroenterology.
Canadian Journal of Gastroenterology 17:25-29, 2002.

39. Abdo AA, **Bain VG**, Kichian K, Lee SS.
Evolution of Autoimmune Hepatitis to Primary Sclerosing Cholangitis: A Sequential Syndrome.
Hepatology 36:1393-1399, 2002.

40. Kichian K, McLean R, Gramlich LM, Bailey RJ, **Bain VG.**
Non-alcoholic Fatty Liver Disease in Patients Investigated for Elevated Liver Enzymes.
Canadian Journal of Gastroenterology 17:38-42, 2003.

41. Greig P, Lilly L, Scudamore C, Erb S, Yoshida E, Kneteman N, **Bain VG**, Ghent C, Marotta P, Grant D, Wall W, Tchervenkov J, Barkun J, Roy A, Marleau D, McAlister V, Peltekian K.
Early steroid withdrawal after liver transplantation: the Canadian tacrolimus versus microemulsion cyclosporin A trial: 1-year follow-up.
Liver Transplantation 9:587-595, 2003.

42. **Bain VG**.
Hepatorenal syndrome, hepatopulmonary syndrome, and now, hepatospinal syndrome?
Liver Transplantation 9:995-996, 2003.

43. Zeuzem S, Heathcote EJ, Shiffman ML, Wright TL, **Bain VG**, Sherman M, Feinman SV, Fried MW, Rasenack J, Sarrazin C, Jensen DM, Lin A, Hoffman JH, Sedarati F.
Twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients treated with interferon alpha for chronic hepatitis C.
Journal of Hepatology 39:106-11, 2003.

44. Dahlan Y, Smith L, Simmonds D, Jewell LD, Wanless I, Heathcote EJ, **Bain VG**.
Pediatric-onset primary biliary cirrhosis.
Gastroenterology 125:1476-1479, 2003.

45. **Bain VG**, Bonacini M, Govindarajan S, Ma M, Sherman M, Gibas A, Cotler SJ, Deschenes M, Kaita K, Jhangri GS.
A Multicentre study of the usefulness of liver biopsy in hepatitis C.
Journal of Viral Hepatitis 11:375-382, 2004.

46. Kneteman NM, Oberholzer J, Al Saghler M, Meeberg GA, Blitz M, Ma MM, Wong WW, Gutfreund K, Mason AL, Jewell LD, Shapiro AM, **Bain VG**, Bigam DL.

Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma.
Liver Transplantation 10:1301-1311, 2004.

47. Shin JL, Teitel J, Swain MG, **Bain VG**, Adams PC, Croitoru K, Peltekian K, Schweiger F, Simmons M, Heathcote J.
A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with a congenital bleeding disorders and hepatitis C: is it safe and useful?
American Journal Hematology. 78:85-93, 2005.

48. Chatur N, Ramji A, **Bain VG**, Ma MM, Marotta PJ, Ghent CN, Lilly LB, Heathcote EJ, Deschenes M, Lee SS, Steinbrecher UP, Yoshida EM.
Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: the Canadian Association for the Study of Liver (CASL) experience with mycophenolate mofetil and tacrolimus.
Liver International 25:723-27, 2005.

49. Romangnuolo J, Andrews CN, **Bain VG**, Bonacini M, Cotler SJ, Ma M, Sherman M
Simple clinical variables predict liver histology in hepatitis C: prospective validation of a clinical prediction model.
Scandinavian Journal of Gastroenterology 40:1365-71, 2005.

50. Bistritz L, Tamboli C, Bigam D, **Bain VG**
Polycystic liver disease: experience at a teaching hospital.
Am J Gastroenterol. 100:2212-7, 2005.

51. Mason A, Theal J, Adams E, Perrillo R, **Bain VG**
Hepatitis B virus replication in damaged endothelial tissues of patients with extrahepatic disease.
Am J Gastroenterol. 100:972-6, 2005

52. Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, Peltekian KM, Lilly LB, Scudamore CH, **Bain VG**, Wall WJ, Roy A, Balshaw RF, Barkun ST.
Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial.
Liver Transpl. 11:1064-72, 2005.

53. Ghali P, Marotta PJ, Yoshida EM, **Bain VG**, Marleau D, Peltekian K, Metrakos P, Deschenes M.
Liver transplantation for incidental cholangiocarcinoma: Analysis of the Canadian experience.
Liver Transpl. 11:1412-6, 2005.

54. Lee SS, **Bain VG**, Peltekian K, Krajden M, Yoshida EM, Deschenes M, Heathcote J, Bailey RJ, Simonyi S, Sherman M.
Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice.

Aliment Pharmacol Ther. 23:397-408, 2006.

55. **Bain VG,** Kaita KD, Yoshida EM, Swain MG, Heathcote EJ, Neumann AU, Fiscella M, Yu R, Osborn BL, Cronin PW, Freimuth WW, McHutchison JG, Subramanian GM
A phase 2 study to evaluate the antiviral activity, safety, and pharmacokinetics of recombinant human albumin-interferon alfa fusion protein in genotype 1 chronic hepatitis C patients.
J Hepatol. 44:671-8, 2006.

56. Mant MJ, **Bain VG**, Maguire CG, Murland K, Yacyshyn BR.
Prevalence of occult gastrointestinal bleeding in celiac disease.
Clinical Gastroenterol Hepatol. 4:451-4, 2006.

57. Sherman M, Yoshida EM, Deschenes M, Krajden M, **Bain VG**, Peltekian K, Anderson F, Kaita K, Simonyi S, Balshaw R, Lee SS
Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy.
Gut. 55:1631-8, 2006.

58. **Bain VG**, Yoshida EM, Kaita KD, Swain MG, Heathcote EJ, Garcia A, Moore PA, Yu R, McHutchison JG, Subramanian GM.
Dynamics of interferon-specific gene expression in peripheral blood of interferon alfa-naive patients with genotype 1 chronic hepatitis C infection treated with albumin-interferon alfa.
Hepatol Res. 35:256-62, 2006.

59. Zeman M, Campbell P, **Bain VG**.
Hepatitis C eradication and improvement of cryoglobulinemia-associated rash and membranoproliferative glomerulonephritis with interferon and ribavirin after kidney transplantation.
Can J Gastroenterol. 20:427-31, 2006.

60. Bistritz L, **Bain VG**.
Sphincter of Oddi dysfunction: Managing the patient with chronic biliary pain.
World J Gastroenterology, 12:3793-3802, 2006.

61. Al-Saif F, Al-Masloom A, Johnson MA, **Bain VG**, Sandha GS, Ritchie DB, Shapiro AM.
Autoimmune pancreatitis with autoimmune hemolytic anemia.
Pancreas. 33:316-7, 2006.

62. McDermid J, Chen M, Li Y, Wasilenko S, Bintner J, McDougall C, Pang X, **Bain VG**, Mason AL.

Reverse transcriptase activity in patients with primary biliary cirrhosis and other autoimmune liver disorders.
Aliment Pharmacol Therapy 26:587-595, 2007.

63. Toso C, Al-Qahtani M, Alsaif FA, Bigam DL, Meeberg GA, Shapiro AM, **Bain VG**, Kneteman N.

ABO-incompatible liver transplantation for critically ill adult patients.
Transplant International, 20:675-681, 2007.

64. Tandon P, Rowe BH, Vandermeer B, **Bain VG**.
The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus.
Am J Gastroenterol 102:1528-1536, 2007.

65. Tandon P, **Bain VG**, Tsuyuki T, Klarenbach S.
Systematic review: renal and other clinically relevant outcomes in hepatorenal syndrome.
Aliment Pharmacol Ther 25:1017-1028, 2007.

66. Toso C, Meeberg G, Bigam DL, Oberholzer J, Shapiro AMJ, Gutfreund K, Ma, MM, Mason AL, Wong WS, **Bain VG**, Kneteman N.
De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects.
Transplantation, 83:1162-1168, 2007.

67. Chatterjee A, Swain MG, Lee SS, **Bain VG**, Peltekian K, Croitoru K, Adams PC, Kaita K, Teitel J, Heathcote EJ.
Induction versus noninduction antiviral therapy for chronic hepatitis C virus in patients with congenital coagulation disorders: a Canadian multicentre trial.
Can J Gastroenterol, 21:91-96, 2007.

68. Demeria D, Birchall I, **Bain VG**.
Dramatic reduction in tumor size in hepatocellular carcinoma patients on thalidomide therapy.
Can J Gastroenterol, 21:517-518, 2007.

69. Powis J, Peltekian KM, Lee SS, Sherman M, **Bain VG**, Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM.
Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3.
Journal of Viral Hepatitis (in press).

70. Karvellas C, Gibney N, Kutsogiannis D, Wendon J, **Bain VG**.
Bench-to-bedside review: current evidence for extracorporeal albumin dialysis systems in liver failure.
Critical Care, 11:215, 2007.

71. Tandon P, Tsuyuki RT, Mitchell L, Hoskinson M, Ma MM, Wong WW, Mason AL, Gutfreund K, **Bain VG**
The effect of 1 month of therapy with midodrine, octreotide-LAR and albumin in refractory ascites: a pilot study.
Liver International, 19, 2008

72. Romagnuolo J, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, **Bain VG,** McKaigney J, Fedorak RN
Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial.
Clinical Gastroenterology Hepatology, 6:4, 465-71, 2008

73. Zeuzem S, Yoshida EM, Benhamou Y, Pianko S, **Bain VG,** Shouval D, Flisiak R, Rehak V, Grigorescu M, Kaita K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG
Albinterferon alfa-2b dosed every two or four weeks in interferon-naïve patients with genotype 1 chronic hepatitis C.
Hepatology, 48:2, 407-17, 2008

74. Alhayaf N, Lalor E, **Bain VG,** McKaigney J, Sandha GS
The clinical impact and cost implication of endoscopic ultrasound on use of endoscopic retrograde cholangiopancreatography in a Canadian university hospital.
Canadian Journal of Gastroenterology, 22:2, 138-42, 2008

75. Powis J, Peltekian KM, Lee SS, Sherman M, **Bain VG,** Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM, Canadian Pegasys Study Group Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3.
Journal of Viral Hepatology, 15:1, 52-7, 2008

76. Kroeker KI, **Bain VG,** Shaw-Stiffel T, Fong TL, Yoshida EM
Adult liver transplant survey: policies towards eligibility criteria in Canada and the United States 2007.
Liver International, 28:9, 1250-5, 2008

77. **Bain VG,** Lee SS, Peltekian K, Yoshida EM, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M, Canadian PEGASYS Study Group
Clinical trial: exposure to ribavirin predicts EVR and SVR in patients with HCV genotype 1 infection treated with peginterferon alpha-2a plus ribavirin.
Aliment Pharmacology Therapy, 29:1, 43-50, 2008

78. **Bain VG,** Kaita KD, Marotta P, Yoshida EM, Swain MG, Bailey RJ, Patel K, Cronin PW, Pulkstenis E, McHutchison JG, Subramanian GM
Safety and antiviral activity of albinterferon alfa-2b dosed every four weeks in genotype 2/3 chronic hepatitis C patients.
Clinical Gastroenterology Hepatology, 6:6, 701-6, 2008

79. Cooper CL, Bailey RJ, **Bain VG,** Anderson F, Yoshida EM, Krajden M, Marotta P, Canadian Pegasys Study Group
Outcomes of peginterferon alpha-2a and ribavirin hepatitis C therapy in Aboriginal Canadians.
Canadian Journal of Gastroenterology, 22:8, 677-80, 2008

80. Rozenberg L, **Bain VG**, McHutchison JG, Pulkstenis E, Subramanian GM, Neumann AU
Pharmacodynamics and viral kinetics during albinterferon alfa-2b therapy of chronic hepatitis C genotype 1 treatment-naive patients.
The Journal of Medicine, 1:1, 2008

81. Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, **Bain VG**, Tandon P
Risk factors for recurrence of autoimmune hepatitis after liver transplantation.
Liver Transplantation, 15:10, 1254-61, 2009

82. Montano-Loza AJ, Tandon P, Kneteman N, Bailey R, **Bain VG**
Rotterdam score predicts early mortality in Budd-Chiari Syndrome, and surgical shunting prolongs transplant-free survival.
Aliment Pharmacol Therapy, 30:10, 1060-1069, 2009

83. Karvellas CJ, Bagshaw SM, McDermid RC, Stollery DE, **Bain VG**, Gibney RT
A case-control study of single-pass Albumin dialysis for acetaminophen-induced acute liver failure.
Blood Purification, 28:3, 151-8, 2009

84. Tandon P, Moncrief K, Madsen K, Arrieta MC, Owen RJ, **Bain VG**, Wong WW, Ma MM
Effects of probiotic therapy on portal pressure in patients with cirrhosis: a pilot study.
Liver International, 29:7, 1110-5, 2009

85. Tandon P, Goodman KJ, Ma MM, Wong WW, Mason AL, Meeberg G, Bergsten D, Carbonneau M, **Bain VG**
A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation.
Am J Gastroenterology, 104:7, 1700-6, 2009

86. Yoshida EM, Sherman M, **Bain VG**, Cooper CL, Deschênes M, Marotta PJ, Lee SS, Krajden M, Witt-Sullivan H, Bailey R, Usaty C, Peltekian K, Pegasys Study Group
Re-treatment with Peginterferon alfa-2a and Ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of Pegylated Interferon-based therapy.
Canadian Journal of Gastroenterology, 23:3, 180-4, 2009

87. Fouad TR, Abdel-Razek WM, Burak KW, **Bain VG**, Lee SS
Prediction of cardiac complications after liver transplantation.
Transplantation, 87:5, 763-70, 2009

88. Neumann AU, **Bain VG**, Yoshida EM, Patel K, Pulkstenis E, Subramanian GM
Early prediction of sustained virological response at day 3 of treatment with Albinterferon-Alpha-2b in patients with genotype 2/3 chronic hepatitis C.
Liver International, 29:9, 1350-5, 2009

89. Carbonneau M, Jensen LA, **Bain VG**, Kelly K, Meeberg G, Tandon P
Alcohol use while on the liver transplant waiting list – a single center experience.
Liver Transplantation, 16:91-97, 2010

90. Asthana S, Maguire C, Lou L, Meier M, **Bain V**, Townsend R, Lien D, Bigam D, Kneteman N, Shapiro A.
Successful resolution of severe hepatopulmonary syndrome following liver transplantation.
Transplant International, 23:432-435, 2010

91. Moncreif KJ, Savu A, Ma MM, **Bain VG**, Wong WW, Tandon P.
The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation – a single centre experience.
Canadian Journal Gastroenterology, 24:1, 40-6, 2010

92. Emamaullee JA, Edgar R, Toso C, Thiesen A, **Bain V**, Bigam D, Kneteman N, Shapiro AM.
Vascular endothelial growth factor expression in hepatic epithelioid hemangioendothelioma: Implications for treatment and surgical management.
Liver Transplantation, 16:191-197, 2010

93. Deschenes M, **Bain VG**, Lee SS, Sherman M, Cooper CL, Yoshida EM, Marotta PJ, Krajden M, Usaty C, Balshaw R, Peltekian KM, Canadian Pegasys Study Group.
Identifying HCV genotype 1 patients at risk of relapse.
European Jouranl Gastroenterology Hepatology, 22:5, 546-51, 2010

94. Meza-Junco J, Montano-Loza AJ, Ma M, Wong W, Sawyer MB, **Bain VG**.
Cholangiocarcinoma: has there been any progress?
Canadian Journal Gastroenterology, 24:1, 52-7, 2010

95. Nelson DR, Benhamou Y, Chuang WL, Lawitz EJ, Rodriguez-Torres M, Flisiak R, Rasenack JW, Kryczka W, Lee CM, **Bain VG**, Pianko S, Patel K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG, ACHIEVE-2/3 Study Team.
Albinterferon Alfa-2b was not inferior to pegylated interferon-? in a randomized trial of patients with chronic hepatitis C virus genotype 2 or 3.
Gastroenterology, 139:4, 1267-76, 2010

96. Jayakumar S, **Bain V**.
Rational Guide to the Use of Erythropoietin in the Treatment of HCV Infection.
Current Hepatitis Reports 10:62-69, 2011

97. Peltekian KM, **Bain VG**, Lee SS, Sherman M, Cooper CL, Yoshida EM, Marotta PJ, Krajden M, Balshaw R, Deschênes M.
Is pre-treatment liver biopsy necessary for all hepatitis C genotypes?
Annals Hepatology 10:260-9, 2011

98. Chopra A, Cantarovich M, **Bain VG**.
Simultaneous liver and kidney transplants: optimizing use of this double resource.
Transplantation 91:1305-9, 2011

99. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, **Bain VG**, Sawyer MB.
Muscle Wasting Is Associated With Mortality in Patients With Cirrhosis.
Clinical Gastroenterology and Hepatology 10:166-73, 2012

100. Meza-Junco J, Montano-Loza AJ, Liu DM, Sawyer MB, **Bain VG**, Ma M, Owen R.
Locoregional radiological treatment for hepatocellular carcinoma; Which, when and how?
Cancer Treat Review 38:54-62, 2012

101. Montano-Loza AJ, Vargas-Vorackova F, Ma M, **Bain VG**, Burak K, Kumar T, Mason AL.
Incidence and risk factors associated with de novo autoimmune hepatitis after liver transplantation.
Liver International 32(9): 1426-33, 2012

102. Ye C, Saincher M, Tandon P, Meeburg G, Williams R, Burak KW, **Bain VG**.
Cardiac work-up protocol for liver transplant candidates: experience from a single liver transplant centre.
Canadian Journal of Gastroenterology 26(11) :806-810, 2012

103. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, **Bain VG**, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP.
Severe muscle depletion in patients on the liver transplant wait list : its prevalence and independent prognosis value.
Liver Transplantation 18(10) : 1209-16, 2012

104. Lambert JE, **Bain VG**, Ryan EA, Thomson AB, Clandinin MT.
Elevated lipogenesis and diminished cholesterol synthesis in patients with hepatitis C viral infection compared to healthy humans.
Hepatology 57(5) :1697-1704, 2013

105. Alameel T, **Bain VG**, Sandha G.
Clinical application of a single-operator direct visualization system improves the diagnostic and therapeutic yield of endoscopic retrograde cholangiopancreatography.
Canadian Journal of Gastroenterology 27(1):15-9, 2013.

106. Kao D, Zepeda-Gomez S, Tandon P, **Bain VG.**
Managing the post-liver transplantation anastomotic biliary stricture: multiple plastic versus metal stents: a systematic review.
Gastrointestinal Endoscopy 77(5):679-91, 2013.

107. Al-Judaibi B, **Bain VG**, Sis B.
An unusual cause of elevated liver enzymes in a diabetic patient.
Gastroenterology 144(7):1354, 1577-8, 2013.

108. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, **Bain VG**, Beaumont C, Esfandiari N, Lieffers JR, Sawyer MB.
Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma
Journal of Clinical Gastroenterology 47(10): 861-870, 2013

109. Jayakumar S, Carbonneau M, Hotte N, Befus AD, St Laurent C, Owen R, McCarthy M, Madsen K, Bailey RJ, Ma M, **Bain V**, Rioux K, Tandon P
VSL#3 probiotic therapy does not reduce portal pressures in patients with decompensated cirrhosis
Liver International 33(10):1470-7, 2013

110. Wells MM. Roth LS. Marotta P. Levstik M. Mason AL. **Bain VG**. Chandok N. Aljudaibi BM.
Increased duration of dual pegylated interferon and ribavirin therapy for genotype 1 hepatitis C post-liver transplantation increases sustained virologic response: a retrospective review
Saudi Journal of Gastroenterology. 19(5):223-9, 2013.

B. Book Chapters and Invited Contributions

1. **Bain VG** and Thomson ABR.
The safety and effectiveness of misoprostol in the treatment of duodenal ulcer.
Internal Medicine for the Specialist 8:73, 1987.

2. **Bain VG** and Thomson ABR.
Update in Small Bowel Disease.
In: Current Gastroenterology Vol 8, Editor G. Gitnick, 1988.

3. **Bain VG** and Thomson ABR.
Gastrointestinal and hepatic complications in the intensive care unit.
Medicine North America 18:3524, 1988.

4. **Bain VG**, Alexander GJM, Eddleston ALWF.
Viral Hepatitis.
In: Immunology and Immunopathology of the Liver and Gastrointestinal Tract.
Eds. Targan S.R. and Shanahan F. 1990.

5. **Bain VG**, Minuk GY.
Jaundice, ascites and hepatic encephalopathy. In:
Oxford Textbook of Palliative Care, Oxford University Press 1993.

6. **Bain VG** (Ed), Depew W, Steinbrecher U.
Hepatitis Update. Would you treat this patient? A debate regarding controversial aspects of chronic hepatitis C and its management.
Canadian Journal of Gastroenterology 10:81, 1996.

7. **Bain VG.**
Hepatitis Update. Literature Review - Hepatitis C current findings - What=s new?
Canadian Journal of Gastroenterology 11:141, 1997.

8. **Bain VG.**
Jaundice, ascites and hepatic encephalopathy.
In: Oxford Textbook of Palliative Medicine,
Oxford University Press, 1997.

9. **Bain VG**, Ma M.
Acute Viral Hepatitis.
In: First Principles of Gastroenterology, Third Ed. Eds, Thomson ABR, Shaffer E, 1997.

10. **Bain VG**, Ma M.
Chronic Hepatitis.
In: First Principles of Gastroenterology, Third Ed. Eds, Thomson ABR, Shaffer E, 1997.

11. **Bain VG.**
Hepatitis C - What does the future hold? (Editorial)
Canadian Journal of Gastroenterology 14:571, 2000.

12. **Bain VG** and Ma M.
Acute Viral Hepatitis
In: First Principles of Gastroenterology, Fourth Ed. Eds. Thomson ABR, Shaffer E, 2000.

13. **Bain VG** and Ma M.
Chronic Hepatitis
In: First Principles of Gastroenterology, Fourth, Ed. Eds. Thomson ABR, Shaffer E, 2000.

14. Lam E and **Bain VG**.
Hepatitis as a World Health Problem.
Encyclopaedia of Life Sciences, Nature Publishing Group, 2001 (www.els.net).

15. Kichian K and **Bain VG.**
Jaundice, ascites and hepatic encephalopathy.
In: Oxford Textbook of Palliative Medicine Oxford University Press 2003.

16. Grover P, **Bain VG**.
Chronic hepatitis.
In: First Principles of Gastroenterology, Fifth Ed. Eds. Thomson ABR, Shaffer E,
2005.

17. **Bain VG.**
Exciting experimental therapies in acute liver failure.
Gastroenterology Canada, Vol 7(3), 2005.

18. **Bain VG**, Tandon P.
Hepatitis as a World Health Problem.
In: Encyclopedia of Life Sciences, Nature Publishing Group, 2006 (www.els.net).

19. **Bain VG**, Tandon P.
Hepatitis as a World Health Problem.
Encyclopedia of Life Sciences, John Wiley & Sons, Ltd: Chichester
http:///www.els.net/[doi:10.1002/9780470015902.a0002236.pub2], 2007.

C. Group Publications

1. **Canadian Association for the Study of the Liver: Hepatitis Consensus Group**.
Treatment of Chronic Viral Hepatitis with Alpha-Interferon: A Consensus Conference Report.
Canadian Journal Gastroenterology 8:179, 1994 and Canadian Journal of Infectious Diseases 5:107, 1994.

2. **The North American Crohn's Study Group Investigators**.
Methotrexate for the treatment of Crohn's disease.
New England Journal of Medicine 332:292, 1995.

3. **Canadian Association for the Study of the Liver Hepatitis Consensus Group**.
Management of viral hepatitis: clinical and public health perspectives - A consensus statement.
Canadian Journal of Gastroenterology 11:407, 1997.

4. Keefe EB, Hollinger FB and **The Consensus Interferon Study Group**.
Therapy of hepatitis C: Consensus interferon trials.
Hepatology 26 (Suppl.)101S, 1997.

5. Tong MJ and **the Consensus Interferon Study Group**.
Treatment of chronic hepatitis C with consensus interferon: A multicentre randomized controlled trial.
Hepatology 26:747, 1997.

6. Heathcote JE, Keefe EB, Lee SS and **the Consensus Interferon Study Group**
Re-treatment of chronic hepatitis C with consensus interferon.
Hepatology 27:1136, 1998.

7. Grant D, Kneteman N, Roy A and **the Canadian Liver Transplant Study Group**.
Peak cyclosporin levels correlate with freedom from liver graft rejection: results of a prospective randomized comparison of neoral and sandimmune for liver transplantation.
Transplantation 67:1133, 1999.

8. Keeffe EB, Dusheiko GM, Tong MJ and **the Consensus Interferon Study Group**.
Genotype does not affect pattern of HCV RNA decrease among responders during interferon

treatment of chronic hepatitis.
Cytokines, Cellular & Molecular Therapy 5:211, 1999.

9. Keeffe EB, Dusheiko GM, James SP and **the Consensus Interferon Study Group**.
Utility of hepatitis C virus serotypes in predicting response to treatment of chronic hepatitis C.
Cytokines, Cellular & Molecular Therapy 5:207, 1999.

10. Grant D, Kneteman N, Tchervenkov J, Roy A, Murphy G, Tan A, Hendricks L, Giulbault N, Levy G.
Peak cyclosporine levels (C max) correlate with freedom from liver graft rejection.
Transplantation 67:1133-1999.

11. Heathcote JE, James S, Mullen KD, Hauser SC, Rosenblate H, Albert Jr DG and **the Consensus Interferon Study Group.**
Chronic hepatitis C virus patients with breakthroughs during interferon treatment can successfully be retreated with consensus Interferon.
Hepatology 30: 562-1999.

12. Wong F, Blei AT, Blendis LM, Thuluvath PJ, for **The North American VPA-985 Study Group.**
A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized placebo-controlled trial.
Hepatology 37:182-190, 2003.

13. Sherman M, **Bain VG**, Villeneuve J-P, Myers RP, Cooper C, Martin S, Lowe C.
The management of chronic viral hepatitis: A Canadian Consensus Conference, www.hepatology.ca, 2004, and Canadian Journal of Gastroenterology 18:715-728, 2004

14. Angeli P, Wong F, Watson H, Gines P and the CAPPS Investigators.
Hyponatremia in cirrhosis: results of a patient population survey.
Hepatology, 44:1535-1542, 2006.

D. Abstracts & Brief Communications (1-100 Thinned – available on request)

101. Chatur N, Ramji A, **Bain VG**, Ma M, Marotta P, Ghent C, Lilly L, Heathcote EJ, Deschenes M, Steinbrecher U, Yoshida E.
Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: The CASL experience with mycophenolate mofetil and Tacrolimus,
American Gastroenterology Association, Feb; M1982, 2004.
Canadian Journal of Gastroenterology. Sep;18:(Suppl A):94A, 2004.

102. Kichian K, Gerhardt A, Gutfreund K, Jewell L, Ma M, Mason AL, Mulesa L, Wong W, **Bain VG**.
The role of the glucose challenge test in the evaluation of patients with non-alcoholic fatty liver disease.

Canadian Journal of Gastroenterology, 18:93A (Suppl A), 2004.

103. Bistritz L, Tamboli C, **Bain VG**.
Polycystic liver disease: Experience at a teaching hospital.
Canadian Journal of Gastroenterology, 18: 93A (Suppl A), 2004.

104. Teitel J, Heathcote EJ, Shin J, Swain MG, **Bain VG**, Adams PC, Croitoru K, Peltekian K, Schweiger F, and Simons ME.
A Canadian multicenter study evaluating transjugular liver biopsy in patients with hepatitis C and congenital bleeding disorders.
Haemophilia. March 10: 46-50 (Suppl 3), 2004.

105. Shin J, Teitel J, Swain M, **Bain VG**, Peltekian K, Croitoru K, Adams P, Simons M, Heathcote EJ.
Risks and benefits of transjugular liver biopsy in patients with congenital coagulation disorders.
Can J Gastroenterol. Feb;18: 87A (Suppl A), 2004.

106. Kichian K, Gerhardt A, Gutfreund K, Jewell L, Ma M, Mason A, Mulesa L, Wong W, **Bain VG**.
The role of the glucose challenge test in the workup of patients with non alcoholic fatty liver disease.
American Gastroenterology Association, T1100, 2004,
Can J Gastroenterol. Feb;18: 93A (Suppl A), 2004.

107. Mathew G, Meeberg G, **Bain VG**, Lalor E, McKaigney J, Kneteman N, Sandha G.
Endoscopic therapy of biliary strictures after orthotopic liver transplantation.
Can J Gastroenterol. 18:(Suppl A):85A, 2004.

108. Feinman SV, **Bain VG**, Peltekian K, Marotta P, Deschenes M.
Efficacy and safety of peginterferon alfa-2a in combination with ribavirin in Canadian patients with chronic hepatitis C: Interim results in cirrhotic and non-cirrhotic patients.
Can J Gastroenterol. Feb;18:(Suppl A):84A, 2004

109. Bain VG.
Clinical trials registry (letter).
Canadian Medical Association Journal 172:979-80, 2005

110. Rozenberg L, **Bain VG**, Neumann AU.
HCV kinetics as function of albuferon pharmacodynamics in subjects with genotype 1 chronic hepatitis C.
12th International Symposium on HCV and Related Viruses, Montreal, Oct 2-6, 2005, Hepatology 2005.

111.Bain VG, Kaita K, Yoshida E, Swain M, Heathcote J, McHutchison J, Neumann A, Bagchi P, Osborn B, Cronin P, Novello L, Freimuth W, Subramanian M.
A phase 2 study to assess antiviral response, safety, and pharmacokinetics of albuferon in IFN-alpha naïve subjects with genotype 1 hepatitis C.
40th Annual Meeting of EASL, Paris, France, Apr 13-17, 2005, Journal of Hepatology

42:(Supplement):9, 2005.

112. Sherman M, Yoshida E, Deschenes M, Krajden M, **Bain VG**, Peltekian K, Anderson F, Kaita K, Simonyi S, Lee S.
Peginterferon alpha-2a (40 kDa) plus ribavirin in chronic hepatitis C patients who failed previous interferon-based therapy: results of a multicenter open-label expanded access program in Canada.
40th Annual Meeting of EASL, Paris, France, Apr 13-17, 2005, Journal of Hepatology.
42:(Supplement):220, 2005.

113. Lee S, **Bain VG**, Peltekian K, Krajden M, Yoshida E, Deschenes M, Heathcote EJ, Bailey R, Simonyi S, Sherman M.
Peginterferon alpha-2a (40 kDa) plus ribavirin in cirrhotic patients with chronic hepatitis C: results of a Canadian Multicentre open-label expanded access program. 2005, Journal of Hepatology 42:(Supplement):209, 2005.

114. Johnson M, **Bain VG**, Bigam D, Gutfreund K, Kneteman N, Mason A, Meeberg G, Shapiro J, Wong W, Ma M.
Liver transplantation for hepatocellular carcinoma: the significance of microvascular invasion and factors associated with cancer recurrence post-liver transplant.
World Congress of Gastroenterology, Sept 10-14, Montreal, QC, 2005.

115. Yoshida E, Heathcote J, Bailey R, Anderson F, Kaita K, Krajden M, Deschenes M, **Bain VG**, Lee S, Sherman M, Peltekian K, Simoni S.
"Real World": experience with peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C: results of a multicenter open-label expanded access program in Canada.
Gastroenterology 128(4, Suppl 2):A723, 2005.

116. Grover PT, Kneteman N, Shapiro J, Bigam D, Ma M, Mason A, Wong W, **Bain VG**, Gutfreund K.
Rapid intrahepatic recurrence of hepatic mangioendothelioma after living donor liver transplantation.
CASL, March, Banff, 2005.

117. Peltekian K, Deschenes M, Lee S, **Bain V**, The Canadian Pegasys Study Group.
Predictability of early virological response to peginterferon alfa-2A (40KD) plus ribavirin in the "Real World".
CASL, March, Banff, 2005.

118.Bain V, Kaita K, Yoshida E, Swain M, Heathcote J, McHutchinson J, Garcia A, Bagchi P, Cronin P, Novello L, Freimuth W, Moor P, Subramanian M.
Interferon specific gene expression mediated by albuferon in IFNA naïve subjects and correlation with anti-viral response.
CASL, March, Banff, 2005.

119. Peltekian K, Deschenes M, Lee S, **Bain V**, The Canadian Pegasys Study Group.
Predictability of early virological response to peginterferon alfa-2A (40KD) plus ribavirin in the

"Real World".
Gastroenterology 128:(4, Suppl 2):A-721, 2005.

120. Burak K, Meeberg G, Myers R, Hilsden R, Swain M, Wong W, Fick G, **Bain VG.**
Should Canada adopt the MELD score for allocation of liver transplants?
Can J Gastroenterol 20:194, 2006.

121. Cooper C, Bailey R, **Bain VG**, Anderson F, Marotta P.
Canada's first nations with chronic hepatitis C: therapeutic outcomes of the pegasys expanded access program.
Can J Gastroenterol 20:197, 2006.

122. Powis J, Peltekian K, Lee S, Sherman M, **Bain VG**, Cooper C, Krajden M, Balshaw R, Heathcote J, Yoshida.
Is it time to separate the management of genotype 2 and genotype 3 in chronic hepatitis C?
Can J Gastroenterol 20:207, 2006.

123.Bain VG, Lee SS, Peltekian K, Yoshida E, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M.
Exposure to ribavirin (RBV) predicts EVR and SVR in patients with HCV genotype 1 infection: analysis of the Canadian pegasys expanded access program (EAP).
Hepatology 44:335A, 2006.

124. McHutchison J, Zeuzem S, Benhamou Y, Shouval D, **Bain VG**, Pianko S et al.
Interim antiviral and safety data with albumin interferon alfa-2B combined with ribavirin in a phase 2B study conducted in a genotype 1, IFN-naïve, chronic hepatitis C population.
Hepatology 44:614A, 2006.

125. Grover PT, Rowe BH, Vandermeer B, **Bain VG**.
The efficacy and safety of bile acid binding agents, opioid antagonists or rifamipin in the treatment of cholestasis associated pruritus.
Hepatology 44:636A, 2006.

126. Nudo C, **Bain VG**, Marleau D, Marotta P, Wong P, Yoshida E et al.
Liver transplantation for hepatic epitheliod hemangioendothelioma and neuroendocrine tumors: the Canadian multicenter experience.
Hepatology 44:411A, 2006.

127. Fiscella M, Balan V, Nelson D, **Bain VG**, Zeuzem S, McHutchison J et al.
Favorable pharmacokinetics of albumin interferon alfa in subjects with chronic hepatitis C.
Hepatology 44:613A, 2006.

128. Zeuzem S, Benhamou Y, **Bain VG**, Shouval D, Pianko S, Flisiak R, Grigorescu M, Rehak V, Yoshida E, Kaia K, Cronin P, Pulkstenis E, Subramanian M, McHutchison J.
Antiviral response at week 12 following completion of treatment with albinterferon α2b plus

ribavirin in genotype 1, IFN-naïve, chronic hepatitis C patients.
J Hepatol 46(Suppl 1):S293, 2007.

129. Deschênes M, Yoshida E, Peltekian K, Cooper C, **Bain VG**, Krajden M, Sherman M, Lee SS, Balshaw R, Marotta P.
Management of chronic hepatitis C in a diverse population with peginterferon α-2a and ribavirin: final results of the Canadian pegasys expanded access program (EAP).
J Hepatol 46(Suppl 1):S232, 2007.

130. Bain VG, Marotta P, Kaita K, Yoshida E, Swain M, Bailey R, Neumann A, Cronin P, McHutchison J, Pulkstenis E, Subramanian M.
Comparable antiviral response rates with albumin interferon alfa-2b dosed at Q2W or Q4W intervals in naïve subjects with genotype 2 or 3 chronic hepatitis C.
J Hepatol 46(Suppl 1):S7, 2007.

131.Bain VG, Lee SS, Peltekian K, Yoshida E, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M.
Exposure to ribavirin (RBV) predicts EVR and SVR in patients with HCV genotype 1 infection: analysis of the Canadian pegasys expanded access program (EAP).
Can J Gastroenterol, 21(Suppl A):155A, 2007.

132. Zeman M, Meeberg G, Belland D, **Bain VG**, Bigam D, Grover P, Gutfreund K, Kneteman N, Mason A, Shapiro J, Wong W, Ma M.
The impact of nutritional status on prediction of outcome in patients awaiting and following liver transplantation.
Can J Gastroenterol 21(Suppl A):146A, 2007.

133. Deschênes M, Lee SS, Cooper C, Marotta P, **Bain VG**, Sherman M, Scully L, Wong D, Balshaw R, Peltekian K.
Is it possible to identify HCV genotype 1 patients at risk of relapse? Analysis of the Canadian Pegasys expanded access program (EAP).
Can J Gastroenterol 21(Suppl A):78A, 2007.

134. Pianko S, Yoshida EM, Zeuzem S, Benhamou Y, **Bain VG**, Pulkstenis E, McHutchison JG, Subramanian GM.
Favorable quality of life (QOL) with albinterferon alfa-2b plus ribavirin in genotype 1, IFN-naïve, chronic hepatitis C (CHC) patients.
Hepatology, 46(Suppl 1):822A, 2007.

135. Zeuzem S, Yoshida EM, Benhamou Y, **Bain VG**, Shouval D, Pianko S, Flisiak R, Grigorescu M, Rehak V, Kaita KD, Cronin P, Pulkstenis E, Subramanian GM, McHutchison JG.
Sustained virologic response rates with albinterferon alfa-2B plus ribavirin treatment in IFN-naive, chronic hepatitis C genotype 1 patients.
Hepatology, 46(Suppl 1):317A, 2007.

136. Romagnuolo J, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, **Bain VG,** McKaigney J, Fedorak RN

Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial.
Clinical Gastroenterology Hepatology, 6:4, 465-71, 2008

137. Stephen Pianko, Eric M. Yoshida, Stefan Zeuzem, Yves Benhamou, **Vincent G. Bain**, et al
Health-Related Quality of Life (HRQOL) with Albinterferon Alfa-2b Plus Ribavirin in IFN Treatment-Naive Patients with Genotype 1 Chronic Hepatitis C.
Gastroenterology, 134:4, 787A, 2008

138. Adivan U. Neumann, Lynn Rozenberg, **Vincent G. Bain,** John G. McHutchison, et al
Viral Kinetics and Pharmacodynamics of Albinterferon Alfa-2b in Interferon Treatment-Naive Patients with Genotype 1, Chronic Hepatitis C.
Gastroenterology, 134:4, 788A, 2008

139. Puneeta Tandon, Karen J. Goodman, Mang M. Ma, Winnie Wong, Andrew L. Mason, Glenda Meeberg, Donna Bergsten, Michelle Carbonneau, **Vincent G. Bain**
The Duration of Pre-Transplant Abstinence is an Independent Predictor of Problem Drinking Post Liver Transplantation
Hepatology, 48:4, 555A-556A, 2008

140. Aldo J. Montano-Loza, Andrew L. Mason, Mang M. Ma, **Vincent G. Bain,** et al
Risk Factors for Recurrene of Autoimmune Hepatitis After Liver Transplantation
Hepatology, 48:4, 1091A-1092A, 2008

141.P Tandon, KJ Goodman, G Meeburg, D Bergstrom, C Hoekstra, M Carbonneau, **VG Bain**
The Duration of Pre-Transplant Abstinence is an Independent Predictor of Problem Drinking Post Liver Transplantation
Gastroenterology, 22, 132A, 2008

142.KI Kroeker, **VG Bain,** T Shaw-Stiffel, T. Fong, et al
Adult Liver Transplant Survey: Policies Towards Eligibility Criteria in Canada and the United States in 2007
Gastroenterology, 22, 125A, 2008

143.P. Tandon, RT Tsuyuki, L. Mitchell, M. Hoskinson, MM Ma, WW Wong, AL Mason, K Gutfreund, **VG Bain**
The Effect of Midodrine, Octreotide and Albumin in Refractory Ascites
Gastroenterology, 22, 120A, 2008

144.J Romagnuolo, R Hilsden, GS Sandha, M Cole, S Bass, G May, J Love, **VG Bain,** J McKaigney, RN Fedorak

Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP): Final Results from a randomized multi-centered placebo-controlled trial

Gastroenterology, 22, 79A, 2008

145.TR Fouad, AAM Shaheen, KW Burak, **VG Bain**, et al
Prediction of Cardiac Complications After Liver Transplantation
Gastroenterology, 22, 81A, 2008

146.K. Moncrief, A. Savu, MM Ma, **VG Bain**, P. Tandon
The Course of Inflammatory Bowel Disease (IBD) and Primary Sclerosing Cholangitis (PSC) After Liver Transplantation for PSC
Gastroenterology, 22, 90A, 2008

147.Y. Benhamou, S. Zeuzem, E. Yoshida, **V. Bain**, et al
Sustained Virologic Response with Albuinterferon Alfa-2b Plus Ribavirin Treatment in IFN-Naïve, Chronic Hepatitis C Genotype 1 Patients
Hepatology International, 2, A167, 2008

148.V. Bain, K. Kaita, P. Marotta, E. Yoshida, M. Swain, R. Bailey, K. Patel, P. Cronin, E. Pulkstenis, J. Mchutchison, M. Subramanian
Albinterferon Alfa-2b Dosed at 4-Week Intervals Demonstrates Clinically Meaningful Antiviral Activity in Chronic Genotype 2 or 3 Hepatitis C Virus Infection: Results of a Phase 2 Study
Hepatology International, 2, A168, 2008

149. Kroeker KI, **Bain VG,** Shaw-Stiffel T, Fong TL, Yoshida EM
Adult liver transplant survey: policies towards eligibility criteria in Canada and the United States 2007
Liver International, 28:9, 1250-55, 2008

150. Nelson D, Benhamou Y, Chuang WL, Lawitz E, Flisiak R, Rodriguez-Torres M, **Bain VG**, Patel K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG
Efficacy and safety results of albinterferon alfa-2B in combination with ribavirin in interferon-alfa treatment naïve patients with genotype 2 or 3 chronic hepatitis C
Journal of Hepatology, 50:1, S378, 2009

151. Sulkowski MS, Zeuzem S, Lawitz E, Grigorescu M, Tice AD, Rustgi VK, Rodriguez-Torres M, Lurie Y, Cianciara J, Bacon BR, **Bain VG**, Kryczka W, Pulkstenis E, Subramanian GM, McHutchison JG,
Efficacy and safety of albinterferon alfa-2B in combination with ribavirin in treatment naive patients with chronic hepatitis C genotype 1
Hepatology, 50:4, 333A, 2009

152. Lambert J, **Bain VG**, Thomson AB, Clandinin MT,
Effectiveness of dietary intervention for liver post-transplant hyperlipidemia
Hepatology, 50:4, 573A, 2009

153. Montano-Loza AJ, **Bain VG**, Ma M, Mason AL
Incidence and risk factors associated with de novo autoimmune hepatitis after liver

transplantation
Hepatology, 50:4, 591A-592A, 2009

154. Benhamou Y, Nelson DR, Chuang W-L, Lawitz E, Flisiak R, Rasenack J, Kryczka W, Lee C-M, Rodriguez-Torres M, **Bain VG**, Schiff ER, Cho M, Janczewska-Kazek E, Peng C-Y, Pulkstenis E
Efficacy and safety results of albinterferon alfa-2B in combination with ribavirin in treatment naive subjects with chronic hepatitis C genotype 2 or 3
Hepatology, 50:4, 1026A, 2009

155. Montano-Loza A, Mason A, Ma M, **Bain VG**, Tandon P
Risk factors for recurrence of autoimmune hepatitis after liver transplantation
The Canadian Journal of Gastroenterology, 23:A, 77A, 2009

156. Ye C, Meghana Saincher M, Tandon P, Meeberg G, Burak KW, **Bain VG**.
Cardiac workup protocol for liver transplant candidates.
Hepatology, 52:4, 842A, 2010

157. Zeuzem S, Pianko S, Foster GR, **Bain V**, Chuang WL, Sarin SK, Flisiak R, Lee CM, Shah SR, Andreone P, Piratvisuth T, Yin Y, Feutren G, Jacobson IM.
Safety and efficacy of Albinterferon-Alfa-2B every four weeks plus ribavirin for treatment of chronic hepatitis C genotype 2/3.
Hepatology, 52:4, 81A, 2010

158. Montano-Loza AJ, **Bain VG**, Mason AL
Incidence and risk factors associated with de novo autoimmune hepatitis after liver Transplantation.
Canadian Journal of Gastroenterology, 24:A, 72A, 2010

159. Peltekian K, **Bain V**, Lee S, Sherman M, Cooper C, Yoshida E, Marotta P, Krajden M, Usaty C, Balshaw R, Deschenes M.
Is pre-treatment liver biopsy necessary in patients with chronic hepatitis C infections?
Canadian Journal of Gastroenterology, 24:A, 157A, 2010

160. Meza-Junco J, Montano-Loza A, Prado C, Lieffers J, Baracos V, **Bain V**, Spratlin J, Sawyer M.
Sarcopenia in Patients (pts) with Hepatocellular Carcinoma (HCC).
Journal of Clinical Oncology, 29: Suppl Abstract e14570

161. Zeuzem S, Pianko S, Foster G, **Bain V**, Chuang W, Sarin S, Flisiak R, Lee C, Shah S, Andreone P, Piratvisuth T, Yin Y, Feutren G, Jacobson M.
Safety and Efficacy of Albinterferon-alfa-2b Every four Weeks Plus Ribavirin for Treatment of Chronic Hepatitis C Genotype 2/3.
AASLD, HCV Clinical Trials Abstract, 2010

162. Brown K, Pianko S, Sarin SK, Jacobson I, Piratvisuth T, Shah S, Andreone P, Lee CM, Gould M, **Bain V**, et al., 2010

Decline in Pulmonary Physiology During Treatment of Chronic Hepatitis C with Long-Acting Interferon and Ribavirin.
Journal of Respiratory Critical Care Medicine, 183, A3040, 2010

163. Montano-Loza A, **Bain V**, Ma M, Mason A.
Incidence and Risk Factors Associated with De Novo Autoimmune Hepatitis After Liver Transplantation.
Canadian Journal of Gastroenterology, 24:A, 72A-73A, 2010

164. Tandon P, Ney M, Irwin I, Ma M, Gramlich L, **Bain V**, Baracos V, Montano-Loza A, Myers R.
Sarcopenia-An Objective Nutritional Assessment Tool that May Facilitate Prioritization of Liver Transplant Candidates.
Hepatology, AASLD Abstracts, 54:4 (Suppl), 665A, 2011

165. Chandok N, Mason A, Adams P, Ma M, **Bain V**, Marotta P, Montano-Loza A.
Assessment of the Optimal Dose of Azathioprine for Patients with Autoimmune Hepatitis.
Hepatology, AASLD Abstracts, 54 :4 (Suppl), 912A, 2011

166. Asthana S, Burak KW, Bailey J, Myers R, Meeberg G, Mason A, **Bain V**, Kneteman N.
Sirolimus-Based Immunosuppression is associated with Improved Sustained Virologic Response (SVR) to Antiviral Treatment for Patients with Recurrent Hepatitis C (HCV) Infection Post-Liver Transplant (LT)
Hepatology, AASLD Abstracts, 54 :4 (Suppl), 451A, 2011

167. Montano-Loza A, Meza-Junco J, Prado C, Lieffers J, **Bain V**, Sawyer M.
Sarcopenia Predicts Early Mortality in Patients with Cirrhosis
Canadian Journal of Gastroenterology, 25:A (Suppl), 73A, 2011

168. Myers R, Faris P, Shaheen A, Aspinall A, Meeberg G, Tandon P, Kneteman N, **Bain V**, Burak K.
Validation of the Five-Variable Model for End-Stage Liver Disease (5VMELD) for Predicting Mortality on the Liver Transplant Waiting List
Canadian Journal of Gastroenterology, 25:A (Suppl), 74A, 2011

169. Cembrowski GS, Tran DV, Higgins TN, Blakney G, **Bain VG**.
Evaluation of serial patient ALT and AST demonstrates 50% more biologic variability in AST : Another reason to stop ordering AST and ALT in tandem.
AACC Annual Meeting, 12-A-1150-AACC, 2012

170. Meza-Junco J, Montano-Loza A, Prado C, Lieffers J, Baracos V, **Bain V**, Sawyer M.
Sarcopenia in patients with hepatocellular carcinoma.
Canadian Journal of Gastroenterology, 26 :(SupplA) :89A, 2012

171. Nelson DR, Lawitz E, **Bain V**, Gitlin N, Hawkins T, Marotta P, Workowski K, Flamm S, Pang PS, McHutchison JG, McNally J, Urbanek P, Yoshida EM.

High SVR12 with 16 weeks of Tegobuvir and GS-9256 with Peginterferon-Alfa 2A and Ribavirin in treatment-naïve genotype 1 HCV patients.
Journal of Hepatology, 56:(Suppl 2), S6-S7, 2012

172. Montano-Loza A, Purdy D, **Bain V**, Meza-Junco J, Ma M, Wong W, Owen R.
Radioembolization with Yttrium-90 for Advanced Hepatocellular Carcinoma: A Canadian Experience.
Journal of Hepatology, 58: S263, 2013

173. Montano-Loza A, Meza-Junco J, Prado C, Tandon P, **Bain V**, Ma M, Beaumont C, Esfandiari N, Sawyer M, Baracos V.
New Cutoff Values for Sarcopenia for Predicting 6-month Mortality in Cirrhotic Patients.
Journal of Hepatology, 58: S221, 2013

174. Alghanem M, Mason A, **Bain V**, Ma M, Kneteman N, Burak K, Montano-Loza A.
Primary Sclerosing Cholangitis Recurs Earlier After Living Donor Liver Transplantation.
Hepatology58:(Suppl 4), 1014A, 2013

175. Selvarajah V, **Bain V**, Ma M, Bhanji R, Montano-Loza A.
Management of Autoimmune Hepatitis in Canada: A National Survey.
Canadian Journal of Gastroenterology, 27:(Suppl A), A180,2013

176. Montano-Loza A, Meza-Junco J, Baracos V, Tandon P, **Bain V**, Ma M, Beaumont C, Esfandiari N, Sawyer M, Kneteman N,
Muscle Wasting is Not Associated with Higher Mortality After Liver Transplantation.
Canadian Journal of Gastroenterology, 27:(Suppl A), A35,2013

177. Jayakumar S, Carbonneau M, Hotte N, Befus D, St. Laurent C, Owen R, McCarthy M, Madsen K, Bailey R, Ma M, **Bain V**, Rioux K, Tandon P.
Probiotics do not Reduce Portal Pressure in Patients with Decompensated Cirrhosis.
Canadian Journal of Gastroenterology, 27:(Suppl A), A31,2013

178.D'Souza P, Montano-Loza A, Halloran B, Teshima C, Zepeda-Gomez S, **Bain V**, Sultanian R, Sandha G.
A Novel Cholangioscopy-Assisted Clinical Subtyping System in Primary Sclerosing Cholangitis – The Edmonton Classification.
Canadian Journal of Gastroenterology, 28:(Suppl A), A61, 2014

179. Montano-Loza A, **Bain V**, Alghanem M, Kneteman N, Burak K.
Primary Sclerosing Cholangitis Recurs Earlier After Living Donor Transplant.
Canadian Journal of Gastroenterology, 28:(Suppl A), A34, 2014

180. Tandon P, Abraldes J, Keough A, Bastiampillai R, Jayakumar S, Carbonneau M, Wong E, Kao D, **Bain V**, Ma M.
The Effect of Antibiotics in Acute Variceal Hemorrhage: A Comparative Effectiveness Study.
Canadian Journal of Gastroenterology, 28:(Suppl A), A58, 2014

181. Bhanji R, Ma M, Bain V, Montano-Loza A.
Early Renal Dysfunction After Liver Transplantation is Associated with Reduced Graft and Patient Survival.
Journal of Hepatology, 60:(Suppl A), 873, 2014

182. Flamm S, Gane E, DuFour J-F, Rustgi V, **Bain V**, Crawford D, et al.
Safety of ABT-450/r/Ombitasvir + Dasabuvir With or Without Ribavirin in HCV Genotype 1-Infected Patients ≥65 Years of Age: Results From Phase 2 and 3 Trials.
Hepatology, 60:(Suppl A), 1157A, 2014

This is Exhibit "B" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta,
this 11 day of MARCH 2015.

A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor

SPECIAL ARTICLE

An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver

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RP Myers, H Shah, KW Burak, C Cooper, JJ Feld. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol 2015;29(1):19-34.

Chronic hepatitis C remains a significant medical and economic burden in Canada, affecting nearly 1% of the population. Since the last Canadian consensus conference on the management of chronic hepatitis C, major advances have occurred that warrant a review of recommended management approaches for these patients. Specifically, direct-acting antiviral agents with dramatically improved rates of virological clearance compared with standard therapy have been developed and interferon-free, all-oral antiviral regimens have been approved. In light of this new evidence, an update to the 2012 Canadian Association for the Study of the Liver consensus guidelines on the management of hepatitis C was produced. The present document reviews the epidemiology of hepatitis C in Canada, preferred diagnostic testing approaches and recommendations for the treatment of chronically infected patients with the newly approved antiviral agents, including those who have previously failed peginterferon and ribavirin-based therapy. In addition, recommendations are made regarding approaches to reducing the burden of hepatitis C in Canada.

Key Words: *Dasabuvir; Direct-acting antivirals; Guideline; Hepatitis C; Interferon; Ledipasvir; Ombitasvir; Paritaprevir; Peginterferon; Simeprevir; Sofosbuvir; Ribavirin; Therapy; Treatment*

Mise à jour sur la prise en charge de l'hépatite C chronique : les lignes directrices consensuelles 2015 de l'Association canadienne pour l'étude du foie

L'hépatite C chronique demeure un fardeau médical et économique important au Canada, car il touche près de 1 % de la population. Depuis la dernière conférence consensuelle canadienne sur la prise en charge de l'hépatite C chronique, on a réalisé des progrès marqués qui justifient une analyse des démarches de prise en charge recommandées. Notamment, on a mis au point des antiviraux à action directe au taux de clairance virologique bien supérieur à celui du traitement standard et on a homologué des antiviraux sans interféron par voie orale. À la lumière de ces nouvelles données probantes, l'Association canadienne pour l'étude du foie a mis à jour les lignes directrices consensuelles 2012 sur la prise en charge de l'hépatite C. Le présent document traite de l'épidémiologie de l'hépatite C au Canada, des démarches et des recommandations favorisées pour traiter les patients atteints d'une infection chronique à l'aide des nouveaux antiviraux homologués, y compris les patients qui n'avaient pas répondu à un traitement à l'interféron pégylé et à la ribavirine. Il contient également des recommandations sur les approches pour réduire le fardeau de l'hépatite C au Canada.

The present guidelines were written to assist physicians and other health care professionals in the management of patients with chronic hepatitis C virus (HCV) infection. They were drafted by Canadian HCV experts at the request of the Executive Committee of the Canadian Association of the Study of the Liver (CASL). The document was made available for review by CASL members and a revised draft based on this feedback was submitted to the Executive Committee of CASL for approval. The information contained within the present guidelines represents a synthesis of evidence from the published literature and scientific abstract presentations available at the time of writing with supplementation by the expert opinions of the authors. Any recommendations should be considered preferred approaches to care rather than strict standards. In some cases, off-label use of regimens are recommended based on the authors' opinions. To more fully characterize the quality of evidence supporting these recommendations, we have assigned a class (reflecting benefit versus risk) and level (assessing strength of certainty) of evidence as adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (1,2), and as used in similar practice guidelines of CASL (3) and the American Association for the Study of Liver Diseases (4) (Table 1). No funding was provided to the authors for this work.

Since the last update of the CASL management guidelines for chronic hepatitis C (CHC) in 2012 (3), major advances have occurred including: the approval of novel direct-acting antiviral agents (DAAs) used with pegylated interferon (PEG-IFN) that have improved efficacy and tolerability compared with first-generation DAAs and/or standard PEG-IFN-based therapy (5-7); and the approval of all-oral, IFN-free, DAA combination therapies with markedly improved efficacy and tolerability and activity beyond just HCV genotype 1 (5,8-15). The current document was developed as an update to previous guidelines with a focus on the management of HCV-infected patients rather than an exhaustive review of CHC or HCV screening. Future guidelines will include 'special populations' with CHC, including people who use injection drugs (PWIDs), incarcerated individuals, patients with decompensated cirrhosis, those pre- or post-transplantation, and patients with HIV/HCV coinfection (for whom relevant guidelines have recently been published by the Canadian Institute of Health Research HIV Trials Network) (16). Due to the rapidity of advances in this field, recommendations in the present document will be updated regularly as new information emerges and novel agents are approved.

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TABLE 1
Grading system for recommendations

Classification	Description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies or standard-of-care

EPIDEMIOLOGY OF HEPATITIS C IN CANADA

CHC remains a significant medical and economic burden in Canada (17-19). In the Canadian Health Measures Survey (20), Statistics Canada and the Public Health Agency of Canada reported an estimated anti-HCV prevalence of 0.5% (95% CI 0.3% to 0.9%) or approximately 138,600 (95% CI 55,800 to 221,300) anti-HCV-positive individuals in Canada. However, these figures are likely underestimates because the Canadian Health Measures Survey excluded several high-risk populations including incarcerated individuals, Aboriginals and PWIDs (20). In fact, a recent modelling study suggests that approximately 252,000 Canadians (uncertainty interval 178,000 to 315,000) were chronically infected in 2013 (18). The peak prevalence was estimated to have occurred in 2003, with approximately 260,000 infected individuals. It has been estimated that approximately 60% of HCV cases in Canada are among current or former PWIDs, 20% are among infected immigrants and 11% have received contaminated blood products (21). Of the nearly 8000 incident cases in Canada in 2007, approximately 80% likely occurred via sharing of injecting equipment, and most of the remainder among immigrants from endemic countries (21). There is wide variation in estimates of the number of HCV-infected individuals who remain undiagnosed. Modelling data from the Public Health Agency of Canada estimated that 79% of individuals were diagnosed in 2003 (21); however, the CMHS found that only 30% of anti-HCV-positive individuals were aware of their infection (20).

Genotype 1 infection is the most prevalent genotype in Canada, representing 65% of infected individuals (56% genotype 1a, 33% genotype 1b, and 10% with an unspecified subtype or mixed infection) (22). The genotype 1 subtype is of relevance for some of the new antiviral regimens due to differing efficacy between genotypes 1a and 1b. Genotypes 2 and 3 account for approximately 14% and 20% of infections in Canada, respectively, whereas genotypes 4, 5 and 6 are very rare (<1% of all infections) (22).

Although the overall prevalence of CHC is declining, complications of CHC are increasing due to aging of the infected population and progression of liver fibrosis (17-19). Modelling data suggest that by 2035, cases of decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality will increase by 80%, 205% and 160%, respectively, compared with 2013 levels (Figure 1) (18). Similarly, annual direct costs associated with CHC (excluding the cost of antiviral therapies) are expected to rise from an estimated $161 million in 2013 to >$258 million at the peak in 2032 (18). Given the alarming estimates of future disease burden, more accurate information regarding the incidence and prevalence of CHC and its sequelae is required to inform health care planning and the allocation of resources. The identification of undiagnosed cases and the dissemination of effective antiviral therapies should be prioritized to reduce complications of this disease (23).

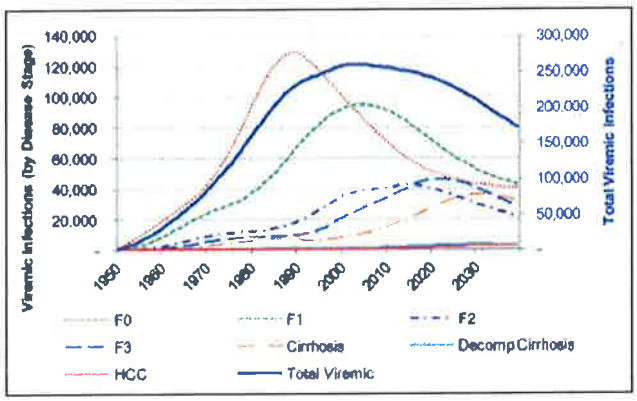


Figure 1) *Modelled incidence of hepatitis C-related sequelae in Canada, 1950 to 2035. Estimates are not mutually exclusive. Reproduced with permission from Myers et al (18). Decomp Decompensated; HCC Hepatocellular carcinoma*

Recommendations:

1. A large population-based seroprevalence survey should be conducted to accurately define the prevalence of hepatitis C in Canada. The design of the study should include populations with an increased risk of hepatitis C, particularly PWIDs, incarcerated individuals and immigrants from endemic countries (Class 2a, Level C).
2. To reduce the future burden of HCV-related morbidity and mortality in Canada, strategies for case identification, harm reduction and disease management – including but not limited to antiviral therapy – should be developed and implemented (Class 2a, Level C).

ANTIVIRAL THERAPY

The primary objective of anti-HCV therapy is complete eradication of the virus, termed a sustained virological response (SVR). SVR has traditionally been defined as undetectable serum HCV RNA at least 24 weeks following the end of treatment (SVR24) (24); however, recent data suggest that earlier assessment at 12 weeks after treatment (SVR12) is sufficient to define this outcome (25). Once achieved, an SVR is considered to be a long-term cure of the virus because late relapses are rare (26,27). SVR is associated with long-term health benefits including improved quality of life (28,29), extrahepatic manifestations of HCV (eg, cryoglobulinemic vasculitis) (30), liver histology (31,32), HCC incidence (33), liver-related morbidity and mortality (34-36), and all-cause mortality (33).

The landscape of antiviral treatment for hepatitis C is changing rapidly. Until recently, the standard therapy was the combination of PEG-IFN and ribavirin (RBV), usually administered for 48 weeks in patients with genotype 1, 4, 5 and 6, and 24 weeks in those with genotypes 2 and 3 (3). Dual therapy achieves SVR rates of 40% to 50% in patients with genotype 1 and approximately 80% in those with genotypes 2, 3, 5 and 6. Results for HCV genotype 4 are intermediate (3). In 2011, the first DAAs, boceprevir (BOC) and telaprevir (TVR), were approved for treatment of HCV genotype 1 in combination with PEG-IFN and RBV. These nonstructural (NS) 3/4A protease inhibitors (PIs) substantially increase rates of SVR in both treatment-naive and previously treated patients compared with dual therapy (37-41). However, they are associated with significant toxicity, complex regimens involving response-guided therapy (RGT), drug-drug interactions (DDIs), and low response rates in patients with cirrhosis and previous treatment failures. In addition, BOC and TVR required coadministration with PEG-IFN and RBV for 24 to 48 weeks, markedly increased the cost of therapy, and are associated with the emergence of resistance-associated variants (RAVs) in the majority of patients who fail treatment (3). The subsequent approval of DAAs with improved efficacy and tolerability, shorter treatment durations, and the option of PEG-IFN- and RBV-free therapy, represents a major advance in the field.

The treatment of CHC is complex and resource intensive. Contributing factors include the high prevalence of psychiatric comorbidities in HCV-infected individuals (eg, depression and addictions), multiple modes of drug administration, side effects, and the requirement for careful on-treatment monitoring of symptoms and laboratory tests. The most successful model to deliver comprehensive CHC care is via a multidisciplinary approach including experienced physicians, nurses and allied health professionals (eg, psychologists, psychiatrists, addiction specialists and social workers). Currently in Canada, a relatively small number of physicians treat CHC, leading in some cases to prolonged wait times for patients to be adequately evaluated and treated. These deficiencies in access to care are greater in rural and remote communities, despite a high HCV prevalence in many regions with limited health care capacity. Moreover, public funding for treatment nurses – who have represented a vital component of the management team – is not universally available. To achieve a meaningful reduction in the future burden of CHC, it will be vital to expand treatment capacity via additional training and funding of experienced personnel and enhanced access to publically funded antiviral therapies (42). With the advent of all-oral antiviral regimens that have few contraindications, minimal toxicity and short treatment courses, the number of patients that can be treated should increase dramatically. However, team-based management will still be necessary to achieve this goal.

Recommendation:

3. Increased resources are necessary to improve hepatitis C treatment capacity in Canada, including the training of expert treaters and public funding for treatment nurses (Class 2a, Level C).

INDICATIONS AND CONTRAINDICATIONS TO ANTIVIRAL TREATMENT

All patients with CHC should be considered candidates for antiviral treatment. The decision of if and when to initiate therapy should be based on the balance between the perceived benefits and risks of treatment and the wishes of the individual patient. Factors to consider include the probability of SVR and the likelihood of progression to advanced liver disease without viral eradication, the presence of extrahepatic manifestations of CHC, the patient's anticipated tolerability of treatment and the life expectancy of the patient. The prospect of new therapies with expected benefits over currently available treatments should also be considered. In light of these issues, prompt initiation of treatment should be considered in certain patient subgroups, especially those with advanced liver fibrosis (F3 or F4 according to the METAVIR classification [bridging fibrosis or cirrhosis]) (43). These patients are at the highest risk of HCV-related complications including liver failure and HCC. Treatment of patients with mild to moderate fibrosis (F1 or F2) should also be considered because progression to more advanced stages is associated with a reduced likelihood of SVR. Moreover, viral eradication in patients at risk of infecting others (eg, PWIDs who continue to share injecting equipment) may reduce the incidence of new infections (44). The curative nature of HCV therapy means that those who achieve SVR before developing cirrhosis do not require long-term follow-up. There are additional benefits to SVR beyond liver disease prevention, including improved quality of life (28,29) and a reduction in all-cause mortality (33). Patients with extrahepatic manifestations of CHC including cryoglobulinemic vasculitis, porphyria cutanea tarda and glomerulonephritis should be considered for treatment regardless of their underlying liver disease severity because these conditions typically respond to viral eradication (30).

TABLE 2
Contraindications for treatment with peginterferon and ribavirin

Absolute contraindications	Pregnancy
Strong, but not absolute, contraindications	Alcohol abuse
	Hepatic decompensation
	Coronary artery disease
	Solid organ transplantation (except liver)
Relative contraindications	Major depression
	Major psychosis
	Autoimmune disease
	Injection drug use
	Renal failure (including dialysis)
Contraindications that are no longer contraindications	Normal alanine aminotransferase
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years of age
	Alcohol use

Table reproduced with permission from (3)

There are very few absolute contraindications to treatment with PEG-IFN- and RBV- based therapy. As postmarketing experience with these therapies has grown, many conditions previously regarded as absolute contraindications are now considered relative, and some may be present only temporarily (Table 2) (3). In most cases, treatment of these patients with PEG-IFN and RBV requires considerable expertise and, therefore, patients with relative contraindications should be treated in expert centres. Contraindications to the recently approved, all-oral regimens are distinctly uncommon.

Recommendations:

4. All patients with chronic HCV infection should be considered candidates for antiviral therapy (Class 1, Level A).
5. Antiviral treatment should be strongly considered in patients with evidence of liver fibrosis (Class 1, Level A).
6. Patients with extrahepatic manifestations of HCV should be considered for antiviral therapy (Class 1, Level A).

PRETREATMENT ASSESSMENT

Routine assessment

The routine assessment of HCV-infected patients should include risk factors for viral acquisition (eg, injection drug use, receipt of potentially contaminated blood products or tissues, and origin from a high-prevalence region), signs and symptoms of advanced liver disease (eg, jaundice, ascites, encephalopathy, portal hypertension-related hemorrhage) or extrahepatic manifestations of CHC, presence of cofactors that may accelerate disease progression (eg, alcohol use, obesity,

TABLE 3
Routine testing of patients with chronic hepatitis C virus (HCV)*

Category of Testing	Tests	Comments
Confirmation and characterization of chronic infection	HCV RNA	Confirms chronicity and baseline for treatment responses
	HCV genotype and subtype	Directs choice of treatment regimen
Assessment of liver disease	Complete blood count	Thrombocytopenia may indicate cirrhosis and portal hypertension. Platelets needed for APRI calculation
	Alanine aminotransferase	Normal value does not preclude significant fibrosis
	Asparatate aminotransferase	Asparatate aminotransferase needed for calculation of APRI
	Gamma-glutamyl transferase	
	Alkaline phosphatase	
	Bilirubin	Elevated bilirubin or INR, or hypoalbuminemia may indicate significant liver dysfunction
	INR (or prothrombin time)	
	Albumin	
	Creatinine	Renal dysfunction increases ribavirin-related hemolytic anemia and may impact drug pharmacodynamics
	Abdominal ultrasound	May suggest cirrhosis, in which case, serves as a baseline for hepatocellular carcinoma surveillance
Viral coinfections	Immunoglobulin G anti-HAV	If negative, vaccinate against hepatitis A
	HBsAg	Exclude hepatitis B coinfection
	Hepatitis B surface antibody	If negative (and HBsAg-negative), vaccinate against hepatitis B
	anti-HIV	Exclude HIV coinfection
Exclude other causes of liver disease†	Alpha-1-antitrypsin	Alpha-1-antitrypsin deficiency
	Ceruloplasmin	Wilson disease.
	Ferritin, serum iron, total iron-binding capacity	Iron overload
	Antinuclear antibody	Autoimmune hepatitis
	Smooth muscle antibody	
	Antimitochrondrial antibody	Primary biliary cirrhosis
	Immunoglobulin G	Often elevated in autoimmune hepatitis and cirrhosis of any cause
	Immunoglobulin A	Often elevated in fatty liver and alcoholic liver disease
	Immunoglobulin M	Often elevated in primary biliary cirrhosis
Contraindications to treatment	Serum or urine β-human chorionic gonadotropin	Exclude pregnancy in women of reproductive age
	Electrocardiogram	If >50 years of age or history of cardiac disease
	Thyroid-stimulating hormone	Exclude thyroid disease, which may be exacerbated by interferon
	Fundoscopy	Exclude retinopathy in patients >50 years of age or with hypertension or diabetes mellitus if interferon is to be prescribed

**Confirmed anti-HCV antibody positive; †Suggested tests only. Tailor testing to individual case. Anti-HAV Antibodies to hepatitis A virus; APRI Aspartate aminotransferase/platelet ratio index; HBsAg Hepatitis B surface antigen; INR International normalized ratio*

coinfections) and potential contraindications to IFN-based therapy (Table 2), which would favour the use of an IFN-free regimen. Necessary laboratory testing includes virological tests to confirm and characterize HCV infection, liver biochemistry, abdominal ultrasound, an assessment of fibrosis stage and tests to rule out coinfections, direct appropriate vaccination and identify contraindications to treatment. In patients with abnormal liver biochemistry, serological tests to exclude coexisting liver diseases should be considered (Table 3).

Virological testing

Approximately one-quarter of patients infected with HCV will clear the virus spontaneously (45). Therefore, chronic HCV infection must be confirmed in all anti-HCV-positive individuals using a sensitive HCV RNA test. HCV RNA detection and quantification using real-time polymerase chain reaction assays is standard due to their sensitivity, specificity, accuracy and broad dynamic range. Results should be expressed in IU/mL and normalized to the WHO international standard. Quantitative assays with a lower limit of detection of approximately 10 IU/mL to 15 IU/mL are recommended. HCV RNA test results should be available within a timely fashion (within seven days) to facilitate management decisions. The rapid identification of failing treatment will reduce patient exposure to costly therapies and potential toxicity, and likely limit the development of RAVs.

The HCV genotype should be assessed in all patients because it has important implications for the decision to initiate treatment and the choice of regimen. With PEG-IFN and RBV therapy, knowledge of only the main genotype (1 to 6) was necessary. However, knowledge of the subtype is now critical, particularly for genotype 1, because of the differing genetic barriers to resistance of HCV subtypes 1a and 1b for many classes of DAAs (46,47). For some DAAs, additional testing (eg, for the Q80K polymorphism [see below]) and/or alternative treatment based on subtype (eg, the use of RBV) may be required.

Recommendations:

7. HCV RNA, genotype, and subtype testing (ie, 1a versus 1b) are essential to the management of patients with chronic hepatitis C (Class 1, Level A).
8. HCV RNA testing should be performed using a sensitive quantitative assay (lower limit of detection of ≤10 IU/mL to 15 IU/mL) with a broad dynamic range. Standardized results should be expressed in IU/mL and be available within a maximum of seven days to facilitate management decisions (Class 1, Level A).

Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is vital for determining the prognosis of HCV-infected patients and the necessity of antiviral treatment. Identification of patients with cirrhosis is particularly important due to their increased risk of hepatic complications, reduced

likelihood of treatment response, and their requirement for surveillance for HCC and esophageal varices. Although the diagnosis of cirrhosis is obvious in some cases based on routine tests (eg, a nodular shrunken liver, splenomegaly or portal hypertensive collaterals on ultrasound), traditionally, liver biopsy has been the reference method for staging fibrosis, determining the severity of other histological lesions (eg, necroinflammation, steatosis) and ruling out coexistent liver diseases (eg, iron overload). Various validated scoring systems have demonstrated sufficient reproducibility and interobserver variability to justify clinical use (eg, METAVIR, Scheuer, Ishak, and Knodell's Hepatic Activity Index) (48). However, liver biopsy has several limitations, including invasiveness and the potential for serious complications including hemorrhage (approximately one in 1000) and death (approximately one in 10,000) (49,50), sampling error and variability in pathological interpretation, high cost, limited availability in many centres, and the difficulty of repeating biopsies to monitor temporal changes in fibrosis. In light of these limitations, numerous noninvasive alternatives to biopsy have been developed (51) including serum markers (eg, the aspartate aminotransferase/platelet ratio index [52]), FibroTest (FibroSure, LabCorp, USA) (53), transient elastography (TE; FibroScan, Echosens, France) (54-57) and other imaging-based tools (58,59).

Although not universally available, a wealth of literature has confirmed that these noninvasive tools can be used instead of liver biopsy to stage HCV-related fibrosis at acceptable levels of accuracy and reproducibility. In a recent survey of Canadian specialists who manage patients with chronic liver disease (60), TE was the primary mode of fibrosis assessment in HCV-infected individuals in 53% of respondents, followed by liver biopsy in 37%. Nearly one-half of respondents estimated that these noninvasive alternatives have reduced their use of liver biopsy by over 50%. In general, these tests are highly accurate for diagnosing cirrhosis and have acceptable, but lower, performance for moderate to severe fibrosis (F2 or greater). The identification of mild fibrosis (F1) and the differentiation between individual stages is poor; however, these limitations also apply to liver biopsy. Emerging data have also demonstrated a correlation between these tests and HCV-related clinical outcomes (61-63), their cost-effectiveness compared with biopsy (64) and responsiveness to viral eradication (65,66). Future studies are necessary to determine the minimal clinically important changes in these markers to facilitate serial monitoring of fibrosis.

Recommendations:

9. Liver fibrosis assessment is vital to the management of patients with CHC (Class 1, Level A).
10. Acceptable methods of fibrosis assessment include liver biopsy, TE (FibroScan) and serum biomarker panels (eg, FibroTest), either alone or in combination. All jurisdictions should provide access to at least one accurate, noninvasive method to assess fibrosis (Class 1, Level A).
11. Alternatively, cirrhosis can be confidently diagnosed in some patients with clear clinical or radiographic evidence (Class 2a, Level C).

Utility of interleukin 28B testing

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene on chromosome 19 that are strongly associated with both spontaneous and treatment-induced HCV clearance (67-70). Patients with the favourable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance compared with heterozygotes (CT) and homozygotes (TT) (67). The CC genotype is also associated with an approximately twofold increase in SVR to PEG-IFN and RBV therapy compared with the unfavourable SNPs in patients with HCV genotype 1 (68,70). The relevance in genotypes 2 and 3 and in treatment-experienced patients is less clear. There is marked ethnic variation in the prevalence of the IL28B genotypes.

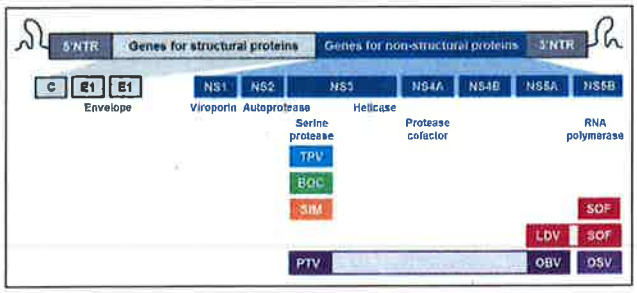


Figure 2) *Hepatitis C virus genome and the polyprotein targets of newly approved, direct-acting antiviral agents. Note: Sofosbuvir (SOF) is a nucleotide nonstructural protein (NS)5B polymerase inhibitor and dasabuvir (DSV) is a non-nucleoside polymerase inhibitor. BOC Boceprevir; LDV Ledipasvir; OBV Ombitasvir; PTV Paritaprevir; SIM Simeprevir; TPV Telaprevir*

The CC genotype is highly prevalent in Asians, but relatively uncommon in Africans, while Caucasians and Hispanics have an intermediate prevalence (68). Similar associations have been reported for the rs8099917 SNP (favourable allele = T and unfavourable allele = G) (71), and for the recently described IFN-lambda 4 (IFNL4) SNP ss46915590 (favourable allele = T and unfavourable allele = ΔG) (72). For simplicity, further discussion will refer to the rs12979860 SNP.

The impact of the IL28B genotype on treatment success is lower when treatment includes DAAs. Patients with the CC genotype have a very high rate of SVR when treated with DAAs plus PEG-IFN and RBV, reaching 98% with sofosbuvir (SOF)-based triple therapy for HCV genotype 1 (5). DAAs lead to a greater relative increase in SVR in non-CC patients. While the IL28B genotype is of limited importance with respect to SVR rates with IFN-free regimens (8,15), whether patients with the favourable IL28B genotype will be able to shorten therapy or use fewer DAAs is unclear.

Recommendations:

12. The IL28B genotype may provide valuable information regarding the likelihood of SVR depending on the HCV genotype and therapy under consideration (Class 2b, Level A).
13. A nonfavourable IL28B genotype does not preclude antiviral therapy (Class 1, Level A).

DAAs

Multiple steps in the HCV life cycle have proven attractive targets for novel pharmacological therapies (Figure 2). Particularly promising agents target the NS3/4A serine protease, the NS5B RNA-dependent RNA polymerase and the NS5A protein (73). The first DAAs approved by Health Canada for the treatment of HCV genotype 1 were the NS3/4A PIs, BOC and TVR. A second-generation PI, simeprevir (SIM), was approved in 2013 for use in combination with PEG-IFN and RBV for genotype 1. In 2013, the first HCV nucleotide polymerase inhibitor, SOF, was approved for use in combination with PEG-IFN and RBV for genotypes 1 and 4 and with RBV alone for genotypes 2 and 3. In 2014, the single-tablet regimen of SOF combined with the NS5A inhibitor ledipasvir (LDV) was approved for patients with HCV genotype 1, including those previously treated with BOC and TVR. In addition, the combination of the ritonavir-boosted PI paritaprevir (PTV_R), the NS5A inhibitor ombitasvir (OBV), and the non-nucleoside polymerase inhibitor dasabuvir (DSV) with or without RBV was approved for patients with HCV genotype 1. Given the markedly improved efficacy and tolerability of these regimens, all patients would benefit from IFN-free therapy. Therefore, these newly approved agents are recommended as first-line therapy for all indications throughout these guidelines. However, access to IFN-free regimens is not universal across Canada. Whether to initiate therapy with an IFN-containing regimen or wait for the availability of all-oral regimens is an individualized decision that must

consider the patient's wishes, the urgency of therapy, the severity of liver disease, the anticipated tolerability of PEG-IFN, the likelihood of SVR and the expected timeline for access to IFN-free regimens.

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1 (TABLE 4)

PEG-IFN-free regimens

SOF/LDV: The nucleotide polymerase inhibitor SOF (400 mg) has been combined with the NS5A inhibitor LDV (90 mg) in a single tablet regimen (SOF/LDV) administered once daily. This combination was evaluated in treatment-naive patients in the open-label ION-1 (8) and ION-3 (10) phase 3 trials with a primary end point of SVR12. In the ION-1 study, which included patients with compensated cirrhosis (16%), participants were randomly assigned to 12 or 24 weeks of SOF/LDV with or without weight-based RBV (8). Among patients who received SOF/LDV for 12 weeks, SVR12 rates were 97% (211 of 217) and 99% (211 of 214) in those who received and did not receive RBV, respectively. In the 24-week treatment arms, SVR12 rates were 99% (215 of 217) in RBV-treated patients compared with 98% (212 of 217) in those who received SOF/LDV alone. There were no statistically significant differences between treatment arms or pretreatment characteristics that were predictive of response. Among the 136 cirrhotic patients, SVR12 rates ranged from 94% to 100%, with no differences between 12 and 24 weeks or with or without RBV. The IL28B genotype was not predictive of response; SVR12 rates ranged from 97% to 99% among patients with the unfavourable non-CC genotype. Only one patient experienced virological breakthrough on therapy and two patients relapsed. All three of these patients had NS5A resistance, but no SOF resistance was detected by deep sequencing. Although the majority of patients complained of at least one adverse event, 93% were mild to moderate in severity with the most common being fatigue, headache, insomnia and nausea. Adverse events were more common in patients randomized to receive RBV. No patient receiving SOF/LDV alone had a hemoglobin concentration <100 g/L.

In the ION-3 study (10), treatment-naive, noncirrhotic patients with HCV genotype 1 were randomly assigned to eight weeks of SOF/LDV with or without weight-based RBV, or SOF/LDV alone for 12 weeks. Among the 215 patients randomly assigned to SOF/LDV for eight weeks, 202 (94%) achieved SVR12, compared with 201 of 216 (93%) who received SOF/LDV/RBV for eight weeks, and 206 of 216 (95%) who received SOF/LDV for 12 weeks. The relapse rates were 5% (SOF/LDV) and 4% (SOF/LDV/RBV) in the eight-week treatment arms and 1% in the 12-week treatment arm. Although the 12-week regimen had a lower relapse rate, treating all patients for an additional four weeks would lead to overtreatment of the majority of individuals. Therefore, a post hoc analysis of baseline viral load was conducted to identify patients in whom an eight-week regimen would suffice (74). In this analysis, patients with an HCV RNA level <6 million IU/mL had a 2% relapse rate in both the eight-week (two of 123) and 12-week (two of 131) SOF/LDV treatment arms, and SVR12 rates of 97% (119 of 123) and 96% (126 of 131), respectively. However, in patients with a baseline viral load ≥6 million IU/mL, those treated for only eight weeks with SOF/LDV had a 10% (nine of 92) relapse rate versus only 1% (one of 85) if treated for 12 weeks. Corresponding SVR12 rates were 90% (83 of 92) and 94% (80 of 85), respectively. Based on these findings, Health Canada and the United States Food and Drug Administration (FDA) have recommended an eight-week regimen of SOF/LDV in treatment-naive, noncirrhotic patients with baseline HCV RNA <6 million IU/mL and 12 weeks in patients with a higher viral load (74).

In addition to baseline viral load, the impact of baseline RAVs on treatment response was examined (10). Although 15 of 23 relapsers (65%) to SOF/LDV had NS5A-resistant variants detected at the time of relapse (present at baseline in nine patients), SOF resistance was not identified. Among 116 patients (18%) with NS5A resistance at baseline, 90% achieved SVR12, suggesting a minimal impact of baseline NS5A RAVs on treatment response with SOF/LDV.

Recommendations:

14. In noncirrhotic, treatment-naive patients with HCV genotype 1, SOF/LDV should be given for eight weeks (Class 1, Level B).
15. In noncirrhotic, treatment-naive patients with genotype 1 and baseline HCV RNA ≥6 million IU/mL, extension of SOF/LDV therapy to 12 weeks can be considered (Class 1, Level C).
16. In cirrhotic, treatment-naive patients with genotype 1, SOF/LDV should be given for 12 weeks (Class 1, Level B).

PTV_R/OBV/DSV ± RBV: The PI PTV is given with low-dose ritonavir (PTV_R) to permit once-daily dosing. PTV_R (150 mg/100 mg) and the NS5A inhibitor OBV (25 mg) are coformulated in a single tablet taken as two tablets once daily. This tablet is combined with the non-nucleoside polymerase inhibitor DSV (250 mg) taken as one tablet twice daily. Placebo or the combination of the three DAAs plus ritonavir (referred to as the '3D' regimen) and weight-based RBV was given for 12 weeks to treatment-naive, noncirrhotic patients with HCV genotype 1 in the phase 3 SAPPHIRE-I trial (15). Patients randomly assigned to placebo subsequently received active treatment. Of 473 patients who started active therapy, 455 (96%) achieved SVR12, clearly superior to a historical control of TVR-based triple therapy in a similar patient population (estimated SVR12 of 78%). SVR12 did

TABLE 4
Treatment-naive patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR

**In noncirrhotic, treatment-naive patients with HCV genotype 1a or 1b, treat with sofosbuvir/ledipasvir (SOF 400 mg/LDV 90 mg) once daily (one tablet) for eight weeks. Consider 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL. + Positive; – Negative; BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; Q80K Simeprevir-associated resistance variant at position 80; RBV Ribavirin (weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM Simeprevir (150 mg once daily); SOF Sofosbuvir (400 mg once daily); TVR Telaprevir*

not differ between patients with HCV genotype 1a (95% [307 of 322]) or 1b (98% [148 of 151]). The only baseline factor associated with response was body mass index (BMI). Obese patients (BMI ≥30 kg/m^2) had an SVR12 rate of 91.5% compared with 97% in patients with a lower BMI. There was no difference in response according to IL28B genotype, fibrosis stage, baseline HCV RNA level, ethnicity or RBV dose modification.

Safety of the regimen was evaluated by comparing with patients randomly assigned to placebo (15). Adverse events were more common in those on active treatment (88%); however, 73% of placebo-treated patients also experienced at least one adverse event. Severe adverse events (2.1%), in particular those requiring drug discontinuation (<1%), were rare. The most common side effects were fatigue and headache, but were no more frequent with active treatment than placebo. Nausea, pruritus, insomnia, diarrhea and asthenia were reported more frequently in patients on active treatment. Total bilirubin elevations were seen in 2.8% of patients on this regimen, likely due to RBV-related hemolysis and inhibition of the bilirubin transporters OATP1B1 and OATP1B3 by PTV_R. No episodes of hepatotoxicity were reported. Grade 2 anemia (hemoglobin 80 g/L to 100 g/L) was reported in 5.8% of patients treated with this regimen including RBV. In 5.5% of patients, the RBV dose was modified due to adverse events, but no impact on the rate of SVR12 was observed in these patients.

The TURQUOISE-II phase 3 trial evaluated the PTV_R/OBV/DSV plus RBV regimen (12 versus 24 weeks) in treatment-naive and treatment-experienced patients with compensated cirrhosis (13). Among treatment-naive patients, the rates of SVR12 were similar between the 12- and 24-week arms (94% [81 of 86] versus 95% [70 of 74]) and by genotype subtype (genotype 1a: 12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]; and genotype 1b: 100% in both the 12-week [22 of 22] and 24-week [18 of 18] groups). SVR12 rates among previously treated patients from TURQUOISE-II are discussed below.

To evaluate the importance of RBV administration with PTV_R/OBV/DSV, the PEARL-III and PEARL-IV phase 3 trials were conducted in treatment-naive, noncirrhotic patients with genotypes 1b and 1a, respectively (75). In PEARL-III, patients with HCV genotype 1b were randomly assigned to receive PTV_R/OBV/DSV alone (n=209) or with RBV (n=210) for 12 weeks. Only three of 419 patients in the trial failed treatment; the SVR12 rate was 99% in both groups. In the PEARL-IV trial, of 205 patients with HCV genotype 1a randomly assigned to receive PTV_R/OBV/DSV alone for 12 weeks, 185 (90%) achieved SVR12; this rate was significantly lower than that observed in patients treated with PTV_R/OBV/DSV plus RBV (97% [97 of 100]), emphasizing the importance of RBV coadministration when this regimen is prescribed to patients with HCV genotype 1a (75).

Recommendations:

17. In treatment-naive patients with HCV genotype 1a infection, with or without cirrhosis, and for those with genotype 1b infection and cirrhosis, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
18. In noncirrhotic, treatment-naive patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).

SOF and SIM: SOF (400 mg daily) was combined with the second-generation PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). The study was divided into two cohorts: cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 87 treatment-naive and null responders with advanced fibrosis (F3 and F4). HCV RNA was suppressed on treatment in all patients, but six patients relapsed. The overall SVR12 rate was 92% (154 of 167), with similar results in cohorts 1 and 2 (90% [72 of 80] versus 94% [82 of 87], respectively). The SVR12 rates did not differ between 12 and 24 weeks of treatment, with or without RBV, or in treatment-naive versus treatment-experienced patients (95% [38 of 40] versus 91% [116 of 127]). The presence of a polymorphism at position 80 with a substitution of a K (lysine) for Q (glutamine), referred to as the 'Q80K' polymorphism, which is associated with reduced activity of SIM and found almost exclusively in patients with HCV genotype 1a (see below) (77,78), did not impact the rate of SVR12 (76). Although four of the six relapsers had genotype 1a infection and the Q80K polymorphism at baseline, 88% (51 of 58) of patients with this polymorphism still achieved SVR12. In this small trial, the regimen was well tolerated; headache, fatigue and nausea were the most commonly reported side effects. Only four patients (2%) discontinued treatment due to adverse events. Although the results from this trial are encouraging, given its small sample size and the availability of other effective and less expensive all-oral antiviral regimens, this regimen should be considered as a second-line option until further data emerge.

Recommendation:

19. In treatment-naive patients with HCV genotype 1a or 1b infection, with or without cirrhosis, SOF (400 mg daily) and SIM (150 mg daily) should be given for 12 weeks without RBV (Class 1, Level B).

PEG-IFN-containing regimens

Given the efficacy and markedly improved tolerability of SOF or SIM combined with PEG-IFN and RBV compared with TVR- or BOC-based regimens, the latter first-generation PIs should no longer be used except in rare circumstances where treatment is urgent and access to newer agents is not available. The use of BOC and TVR is reviewed in the 2012 version of the present guidelines (3).

SOF, PEG-IFN and RBV: SOF (400 mg daily) was combined with PEG-IFN and RBV for 12 weeks in patients with HCV genotypes 1, 4, 5 and 6 in the uncontrolled, open-label, phase 3 NEUTRINO trial (5). Among patients with HCV genotype 1, the SVR12 rate was 89% (261 of 292). Although a higher proportion of patients with genotype 1a achieved SVR12 than those with genotype 1b (92% [206 of 225] versus 82% [54 of 66]), this difference was not statistically significant. In multivariate analysis, the presence of cirrhosis and a non-CC IL28B genotype were the only predictors of virological failure. The SVR12 rate was 92% (252 of 273) in noncirrhotic patients versus 80% (43 of 54) in patients with compensated cirrhosis. The SVR12 rate was 98% (93 of 95) in patients with the IL28B CC genotype, compared with 87% (202 of 232) in those with a non-CC genotype. Although the side effect profile appeared similar to that of PEG-IFN and RBV dual therapy, the uncontrolled nature of the study precluded a clear evaluation of safety. However, only 2% of patients discontinued treatment due to an adverse event. Among the 28 patients who relapsed (9% of the cohort), resistance to SOF was not detected by deep sequencing (5).

Recommendation:

20. In patients with HCV genotype 1a or 1b, with or without cirrhosis, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).

SIM, PEG-IFN and RBV: In the QUEST-1 and QUEST-2 phase 3 trials (6,7), conducted in North America and Europe, respectively, the second-generation PI SIM (150 mg once daily) was combined with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 or 36 weeks of PEG-IFN plus RBV and compared with PEG-IFN plus RBV for 48 weeks in patients with HCV genotype 1. Patients randomly assigned to triple therapy who had HCV RNA <25 IU/mL at week 4 and undetectable HCV RNA at week 12 continued PEG-IFN plus RBV for 12 additional weeks and then stopped all treatment. Patients who did not meet these early response criteria continued PEG-IFN and RBV for an additional 36 weeks (ie, 48 weeks total). In pooled data from these trials, the SVR12 rate in the SIM/PEG-IFN/RBV groups was 80% (419 of 521), significantly higher than in

patients receiving PEG-IFN and RBV alone (50% [132 of 264]) (6,7). In total, 88% (459 of 521) of patients in the SIM/PEG-IFN/RBV groups qualified for shortened therapy and 88% (405 of 459) of these patients achieved SVR12. In the two trials, of the 12% (62 of 521) of patients who did not qualify for shortened therapy, the SVR12 rate was 32% despite up to 36 weeks of additional PEG-IFN and RBV. SVR12 rates differed according to baseline fibrosis level, decreasing from 84% (317 of 378) in patients with F0 to F2 fibrosis to 60% (29 of 48) in those with cirrhosis. The IL28B genotype was also important, with SVR12 rates of 95% (144 of 152) in CC patients treated with triple therapy compared with 80% (63 of 79) with PEG-IFN and RBV alone, and 75% (275 of 369) in patients with a non-CC genotype who received triple therapy compared with 37% (69 of 185) in the control arm.

The most important predictor of response was the presence of the Q80K polymorphism at baseline (described above). In pooled data from these trials (6,7), the SVR12 rate with SIM-based triple therapy was 58% (49 of 84) in patients with genotype 1a and Q80K; no different than that seen in the PEG-IFN and RBV control arm (52% [23 of 44]). In contrast, among patients with genotype 1a infection without Q80K, the SVR12 rate was 84% (138 of 165), similar to that seen in patients with genotype 1b infection (85% [228 of 267]) and significantly higher than found in the control arms (43% [36 of 83] in genotype 1a without Q80K and 53% [70 of 133] in genotype 1b). In these trials, the Q80K polymorphism was present at baseline in 34% of patients with genotype 1a infection and available sequencing data, but in only one of 400 patients with genotype 1b (6,7). Rates of Q80K positivity among patients with HCV genotype 1a in Canada have been reported to be as high as 47% (79).

SIM was well tolerated in these trials (6,7). In pooled data across the SIM study program (80), the main adverse events seen more frequently in SIM-treated patients were rash (mostly mild) seen in 23% of patients (versus 17% of controls) and photosensitivity in 3.3% (versus 0.5% of controls). Total bilirubin elevation, which is due to inhibition of biliary transporters and RBV-related hemolytic anemia, was observed in 7.9% of patients (versus 2.8% of controls). Notably, the incidence of anemia was similar among patients treated with SIM-based triple therapy versus PEG-IFN and RBV alone.

Recommendations:

21. In patients with HCV genotype 1b infection and patients with genotype 1a infection without the Q80K polymorphism, SIM (150 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks followed by an additional 12 weeks of PEG-IFN plus RBV (Class 1, Level A).
22. Patients with genotype 1a infection must be tested for the Q80K polymorphism before starting therapy with SIM, PEG-IFN and RBV. Patients with the Q80K polymorphism should be treated with an alternative regimen (Class 1, Level A).
23. RGT should not be used with SIM, PEG-IFN and RBV. Patients who have HCV RNA ≥25 IU/mL at week 4 or detectable HCV RNA at week 12 should stop all therapy given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV (Class 2b, Level C).

TREATMENT-EXPERIENCED PATIENTS WITH HCV GENOTYPE 1 (TABLE 5)

PEG-IFN-free regimens

Patients who have failed IFN-based therapy should be categorized as relapsers (undetectable HCV RNA during treatment with reappearance of HCV RNA within six months of stopping therapy), partial responders (decline of at least 2 $\log_{10}$ IU/mL in HCV RNA without ever achieving undetectable HCV RNA during therapy), or null responders (<2 $\log_{10}$ IU/mL decline in HCV RNA during therapy; or breakthrough [increase by >1 $\log_{10}$ IU/mL in HCV RNA above nadir despite ongoing antiviral therapy]) (3). Patients with an unknown previous response should be managed as null responders. As in treatment-naive patients, all previously treated patients with HCV genotype 1 would benefit from all-oral DAA regimens rather than those containing IFN because these patients, with the exception of relapsers, have demonstrated poor IFN responsiveness.

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in treatment-experienced patients in the ION-2 phase 3 trial (9). The study included relapsers (56%) and nonresponders (44%), including patients who had failed PEG-IFN/RBV dual therapy (48%) or in combination with a PI (52%). Patients were randomly assigned to receive 12 or 24 weeks of treatment with or without weight-based RBV. The SVR12 rate was 94% (102 of 109) in patients who received 12 weeks of SOF/LDV and 96% (107 of 111) in those who also received RBV. The SVR12 rate in patients who received 24 weeks of SOF/LDV therapy was 99% (218 of 220 overall) whether the patients also received RBV. Virological relapse occurred in 4% to 6% of patients treated for 12 weeks, but in none treated for 24 weeks. The SVR12 rate in patients with compensated cirrhosis (20% of each treatment arm) treated for 12 weeks with SOF/LDV alone was 86% (19 of 22) versus 82% (18 of 22) in those who also received RBV. In cirrhotic patients treated for 24 weeks (with or without RBV), the SVR12 rate was 100% (44 of 44). No baseline or on-treatment predictors of relapse were identified in patients with cirrhosis. There were no differences in SVR12 rates according to receipt of RBV, previous antiviral regimen (PEG-IFN/RBV versus PEG-IFN/RBV plus a PI), or previous treatment response (relapse versus nonresponse). Among the 62 patients (14%) with detectable NS5A resistance at baseline, 55 (89%) achieved an SVR12. All 11 patients who relapsed had detectable NS5A resistance at the time of relapse, but SOF-associated resistance was not detected. Among patients previously treated with a PI-containing regimen, 71% had NS3/4A resistance at baseline and 98% of these patients achieved an SVR12 (9). Tolerability of SOF/LDV was similar to that observed in the ION-1 and ION-3 studies (see above) (8,10); more adverse events were reported in patients treated with RBV.

Based on the higher rates of response observed in the ION-2 trial among previous treatment failure patients with compensated cirrhosis treated for 24 versus 12 weeks, Health Canada and the FDA have recommended a 24-week regimen of SOF/LDV in this patient subgroup. However, a subsequent and significantly larger randomized trial from France (the SIRIUS trial) (81) suggested that a 12-week regimen of SOF/LDV plus weight-based RBV is as effective as a 24-week SOF/LDV regimen in patients with cirrhosis who had failed both PEG-IFN/RBV and triple therapy including a PI. Specifically, 74 of 77 patients (96%) randomly assigned to SOF/LDV/RBV for 12 weeks had an SVR12 (4% relapse rate) compared with 75 of 77 patients (97%) randomly assigned to SOF/LDV alone for 24 weeks (3% relapse rate). Furthermore, in a pooled analysis of data from the SIRIUS trial and six other phase 2 and 3 studies that included 352 treatment-experienced patients with cirrhosis (82), 12 weeks of SOF/LDV/RBV resulted in a similar SVR12 rate to 24 weeks of SOF/LDV alone (96% versus 98%).

Recommendations:

24. In noncirrhotic patients with HCV genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV without RBV should be given for 12 weeks (Class 1, Level B).
25. In cirrhotic patients with genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV and weight-based RBV should be given for 12 weeks (Class 1, Level A).

PTV_R/OBV/DSV and RBV: The combination of PTV_R/OBV/DSV with weight-based RBV was evaluated in treatment-experienced patients without cirrhosis in the SAPPHIRE-II phase 3 trial (14). Among 297 patients randomly assigned to PTV_R/OBV/DSV plus RBV regimen for 12 weeks, 286 (96%) achieved SVR12. No pre- or on-treatment predictors of response were identified. The SVR12 rate was

TABLE 5
Treatment-experienced patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24–48 weeks†,‡	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12–24 weeks*	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks†‡	PEG/RBV/BOC or TVR

**Patients with HCV genotype 1a, cirrhosis and previous null response should receive 24 weeks of PTV_R/OBV/DSV/RBV (paritaprevir/ritonavir/ombitasvir/dasabuvir/ribavirin) if treated with this regimen. Relapsers and partial responders with genotype 1 and cirrhosis can be treated for 12 weeks with PTV_R/OBV/DSV/RBV; †Simeprevir (SIM)-containing regimens should not be given to patients who have failed previous therapy with a protease inhibitor; ‡Previous null responders with genotype 1a or 1b should not be treated with SIM/ Peginterferon alfa-2a or peginterferon alfa-2b (PEG)/RBV regardless of the presence or absence of cirrhosis. Previous relapsers should be treated for 24 weeks total (12 weeks of SIM/PEG/RBV followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial responders should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. + Positive; – Negative; BOC Boceprevir; DSV: 250 mg one tablet twice daily; IFN Interferon; PEG: Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV: 150 mg/100 mg/25 mg, two tablets once daily; Q80K SIM-associated resistance variant at position 80; RBV weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg; SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet); TVR Telaprevir*

similar between patients with genotype 1a (96% [166 of 173]) and 1b (97% [119 of 123]), and did not differ between relapsers (95% [82 of 86]), partial responders (100% [65 of 65]) and null responders (95% [139 of 146]). RAVs to one or more of the three DAAs in the regimen were detected in five of the seven patients with post-treatment relapse (14).

In the TURQUOISE-II trial (13), PTV_R/OBV/DSV plus RBV regimen for 12 or 24 weeks was evaluated in 380 patients with compensated cirrhosis, of whom 58% had previously failed PEG-IFN and RBV therapy. Among patients with genotype 1b, the SVR12 rate was 99% (67 of 68) with 12 weeks of therapy and 100% (51 of 51) with 24 weeks. Response rates did not differ according to treatment duration or previous treatment history. In patients with genotype 1a infection, SVR12 rates were 89% (124 of 140) with 12 weeks and 94% (114 of 121) with 24 weeks of therapy; this difference was not statistically significant. There was no difference between the 12- and 24-week study arms among treatment-naive, cirrhotic patients with genotype 1a (12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]), previous relapsers (93% [14 of 15] versus 100% [13 of 13]) or partial responders (100% [11 of 11] versus 100% [10 of 10]). However, among null responders with genotype 1a, the 24-week arm was superior to 12 weeks of treatment (93% [39 of 42] versus 80% [40 of 50]) (13).

To determine the importance of RBV in noncirrhotic, treatment-experienced patients with HCV genotype 1b infection, the PEARL-II study randomly assigned patients to receive PTV_R/OBV/DSV with or without RBV for 12 weeks (83). All 91 patients (100%) who received PTV_R/OBV/DSV alone achieved SVR12 compared with 97% (85 of 88) randomly assigned to also receive RBV.

There is expected to be overlap between RAVs due to PI-based therapies. Because the PTV_R/OBV/DSV regimen contains a PI and other regimens with documented activity in these patients are available (ie, SOF/LDV) (9), this regimen should not be used in patients who have failed another PI (eg, TVR, BOC or SIM).

Recommendations:

26. In noncirrhotic, treatment-experienced patients with HCV genotype 1a infection, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
27. In noncirrhotic, treatment-experienced patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).
28. In cirrhotic patients with genotype 1a infection and a history of previous null response to PEG-IFN and RBV, coformulated PTV_R/OBV/DSV should be given with RBV for 24 weeks (Class 1, Level B).
29. In patients who have failed therapy with another PI, coformulated PTV_R/OBV/DSV should not be given due to the potential for cross-resistance with PTV (Class 2b, Level C).

SOF and SIM: As previously described, SOF (400 mg daily) was combined with the PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). Cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 47 null responders (plus 40 treatment-naive patients) with advanced fibrosis (F3 and F4). Overall, 116 of 127 null responders (91%) achieved an SVR12, not significantly different from that observed among treatment-naive subjects (95% [38 of 40]). SVR12 rates among null responders were similar regardless of fibrosis severity (F0 to F2: 90% [72 of 80] versus F3: 96% [23 of 24] versus F4: 91% [21 of 23]), treatment duration or receipt of RBV. Given the expected cross-resistance between other PIs and SIM, patients who previously failed treatment with these agents were excluded from the study (76). Because of the small sample size of this trial and the availability of other effective and less expensive IFN-free regimens, this combination should be considered as a second line option until further data emerge.

Recommendations:

30. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV, SOF (400 mg daily) and SIM (150 mg daily) should be given without RBV for 12 weeks (Class 1, Level B).
31. The combination of SOF and SIM should not be used in patients who have failed therapy with another PI (Class 2b, Level C).

PEG-IFN-containing regimens

Given the efficacy and markedly improved safety and tolerability of SOF and SIM combined with PEG-IFN and RBV compared to TVR or BOC-based regimens, these first generation PIs should no longer be used except in rare circumstances (see above).

SOF, PEG-IFN and RBV: Experience with the use of SOF (400 mg) in combination with PEG-IFN and RBV in patients who have failed IFN-based therapy is limited. Nevertheless, Health Canada and the United States FDA have approved this regimen for treatment-experienced patients. Based on a modelling approach, the FDA projected an SVR12 rate of 78% in PEG-IFN and RBV treatment failures if retreated with SOF plus PEG-IFN/RBV for 12 weeks. In the NEUTRINO phase 3 trial of treatment-naive patients (5), 52 patients with HCV genotype 1 had characteristics typical of the treatment-experienced population (ie, advanced fibrosis [F3 and F4], a non-CC IL28B genotype and high baseline viral load [≥800,000 IU/mL]). Thirty-seven of these patients (71%) achieved SVR12 with 12 weeks of SOF/PEG-IFN/RBV (74). Although this regimen is also untested in patients who have failed therapy with a PI, the absence of cross-resistance between the PIs and SOF suggests that these patients should respond similarly to those who failed treatment with PEG-IFN/RBV alone.

Recommendation:

32. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV with or without a PI, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 2b, Level C).

SIM, PEG-IFN and RBV: SIM (150 mg daily) has been evaluated in combination with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 to 36 weeks of PEG-IFN and RBV in patients with HCV genotype 1 who failed IFN-based therapy in two trials. The phase 3 PROMISE study (84) included relapsers, whereas the phase 2b ASPIRE trial (85) also included partial and null responders. In the PROMISE trial (84), an RGT approach identical to that used in treatment-naive patients was evaluated (see above). Treatment with triple therapy was more effective than PEG-IFN and RBV dual therapy (SVR12: 79% [206 of 260] versus 36% [48 of 133]) in these relapsers. The majority of SIM-treated patients (93% [241 of 260]) were eligible to shorten treatment from 48 to 24 weeks and 83% of these patients (200 of 241) achieved SVR12. In patients with undetectable HCV RNA at week 4 (77% of the cohort), the SVR12 rate was 87% (173/200), compared with 60% in those with HCV RNA <25 IU/mL but detectable at week 4. Among patients who did not qualify for shortened therapy, the SVR12 rate was 40% (six of 15) despite 48 weeks of treatment. Of the 39 patients with compensated cirrhosis randomly assigned to triple therapy, 29 (74%) achieved SVR12 compared with five of 19 (26%) in the control arm. As reported in treatment-naive subjects from the QUEST-1 and QUEST-2 trials (6,7), patients with HCV genotype 1a and the Q80K mutation at baseline did not benefit from SIM treatment (SVR12 rates in the simeprevir and placebo arms: 47% [14 of 30] versus 30% [six of 20], respectively). RAVs similar to those selected by TVR and BOC emerged in most patients (90%) who did not achieve SVR12 in the SIM arm (84).

In the phase 2b ASPIRE trial (85), 462 patients who failed PEG-IFN/RBV therapy (40% relapsers, 35% partial responders and 25% null responders) were randomly assigned to receive SIM (100 mg or 150 mg or placebo) for 12, 24 or 48 weeks in combination with PEG-IFN and RBV for 48 weeks. In patients treated with SIM 150 mg daily for 12 weeks, SVR24 rates were 77% (20 of 26) in relapsers, 65% (15 of 23) in partial responders and 44% (eight of 18) in null responders; all superior to rates in the control arm (37%, 19% and 9%, respectively). Among null responders with cirrhosis (across all SIM 150 mg arms), 31% (four of 13) achieved SVR24 with SIM compared with neither of two patients treated with PEG-IFN and RBV.

Recommendations:

33. In patients with HCV genotype 1b or genotype 1a infection without the Q80K polymorphism who relapsed to PEG-IFN and RBV, SIM (150 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks followed by PEG-IFN plus RBV for an additional 12 weeks. All therapy should be discontinued in patients who have HCV RNA >25 IU/mL at week 4 or detectable HCV RNA at week 12 (Class 1, Level A).
34. In patients with previous partial or null response, alternative regimens should be considered given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV with this regimen (Class 2b, Level B).

PATIENTS WITH HCV GENOTYPE 2 (TABLE 6)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) was administered in combination with weight-based RBV for 12 weeks to treatment-naive patients with HCV genotype 2. Patients randomly assigned to the control arm received a 24-week course of PEG-IFN and RBV (800 mg daily). Patients with cirrhosis accounted for approximately 20% of the study population. The SVR12 rates in the SOF/RBV and PEG-IFN/RBV arms were 97% (68 of 70) and 78% (52 of 67), respectively. The incidence of adverse events was consistently lower among patients who received SOF/RBV, particularly the influenza-like symptoms and depression characteristic of IFN-based therapy. In the phase 3 VALENCE trial (12), 32 treatment-naive patients with HCV genotype 2 received a 12-week regimen of SOF and weight-based RBV. As observed in the FISSION study (5), all but one of these patients (97%) achieved an SVR12. The response rate did not differ between cirrhotic (100% [two of two]) and noncirrhotic patients (97% [29 of 30]). In the phase 3 POSITRON trial (11), 143 IFN-ineligible patients with HCV genotype 2 were randomly assigned to receive SOF and weight-based RBV for 12 weeks or placebo. The majority of patients in this trial had contraindications to or refused IFN therapy; only 7% had previously

TABLE 6
Patients with hepatitis C virus genotype 2

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-experienced, noncirrhotic	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 16 weeks*	None	PEG/RBV/PI
				SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM

**Clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet)*

failed IFN-based treatment. Among 109 patients with genotype 2 treated with SOF/RBV for 12 weeks, 101 patients (93%) achieved an SVR12, similar to results observed in the FISSION and VALENCE trials (5,12). SVR12 rates did not differ between patients with and without cirrhosis (94% [16 of 17] versus 92% [85 of 92]).

SOF (400 mg daily) and weight-based RBV has also been studied in treatment-experienced patients with HCV genotype 2 in the VALENCE (12) and FUSION (11) phase 3 trials. In VALENCE (12), 37 of 41 (90%) treatment-experienced patients had an SVR12 following a 12-week course of SOF/RBV. In the FUSION trial (11), 68 patients who had previously failed an IFN-containing regimen (approximately 75% due to relapse), were randomly assigned to receive SOF/RBV for either 12 or 16 weeks. Overall, an SVR12 was observed in 86% (31 of 36) of patients treated for 12 weeks versus 94% (30 of 32) treated for 16 weeks, although this difference was not statistically significant. In patients without cirrhosis, high rates of SVR12 were observed regardless of treatment duration (12 versus 16 weeks: 96% [25 of 26] versus 100% [23 of 23]). However, lower rates of response were observed among patients with cirrhosis (12 versus 16 weeks: 60% [six of 10] versus 78% [seven of nine]). Although this difference was not statistically significant, the poor response rate among patients treated for 12 weeks suggests that a 16-week regimen is preferred if SOF/RBV is prescribed to this patient subgroup, particularly in IFN-ineligible subjects. Tolerability of SOF/RBV was similar to that observed in the FISSION and POSITRON studies (5,11).

SOF, PEG-IFN and RBV

SOF, PEG-IFN, and weight-based RBV for 12 weeks has been studied in patients with HCV genotype 2 who failed previous therapy in an open-label phase 2 study (86). Among 23 patients with HCV genotype 2 (14 with cirrhosis), an SVR12 rate of 96% (22 of 23) was observed. High rates of response were observed among cirrhotic (93% [13 of 14]) and noncirrhotic patients (100% [nine of nine]). Among the entire study population (n=47), which also included 24 patients with genotype 3, three patients discontinued RBV due to anemia and one patient discontinued all therapy due to pain. Serious adverse events occurred in four patients (9%); the majority were considered due to PEG-IFN or RBV and none due to SOF.

Recommendations:

35. In treatment-naive patients with HCV genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
36. In noncirrhotic, treatment-experienced patients with genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
37. In IFN-eligible, treatment-experienced patients with genotype 2 and cirrhosis, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks. In IFN-ineligible patients, SOF (400 mg daily) should be given with weight-based RBV for 16 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPE 3 (TABLE 7)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) in combination with weight-based RBV for 12 weeks or PEG-IFN/RBV (800 mg daily) for 24 weeks were administered to 359 treatment-naive patients with HCV genotype 3. Overall, an SVR12 was observed in 56% (102 of 183) of patients randomly assigned to receive SOF/RBV compared with 63% (110 of 176) in those treated with PEG-IFN/RBV. This difference was not statistically significant. In light of the suboptimal responses observed with a 12-week SOF/RBV regimen in this trial, the VALENCE trial examined a 24-week course in patients with HCV genotype 3 (12). Among treatment-naive patients, 94% (99 of 105) achieved an SVR12; responses did not differ between cirrhotic (92% [12 of 13]) and noncirrhotic patients (95% [87 of 92]).

SOF/RBV combination therapy has also been studied in treatment-experienced patients with HCV genotype 3. In the FUSION phase 3 trial (11), 127 patients who had failed previous treatment were randomly assigned to 12 or 16 weeks of SOF and weight-based RBV. Overall, SVR12 rates were 30% (19 of 64) and 62% (39 of 63) in the 12- and 16-week groups, respectively. The presence of cirrhosis was a strong negative predictor of response in patients treated for 12 weeks; only 19% (five of 26) of cirrhotic patients and 37% (14 of 38) of noncirrhotic patients had an SVR12 with this regimen. In the 16-week treatment arm, SVR12 rates were 61% (14 of 23) among patients with cirrhosis and 63% (25 of 40) in those without cirrhosis. In this trial, the primary mode of treatment failure was relapse, which was observed among 66% (42 of 64) of patients treated for 12 weeks and 38% (24 of 63) of those treated for 16 weeks. Therefore, the VALENCE trial examined a longer course (24 weeks) of SOF/RBV therapy in 145 treatment-experienced patients with HCV genotype 3 (12). Among 98 noncirrhotic patients in this trial, an SVR12 was observed in 85 (87%). However, only 62% (29 of 47) of patients with cirrhosis had an SVR12. Based on these data, alternative treatment options are necessary in cirrhotic, treatment-experienced patients with HCV genotype 3.

SOF, PEG-IFN and RBV

SOF, PEG-IFN and weight-based RBV administered for 12 weeks was studied in patients with HCV genotype 3 who failed previous therapy in a small, open-label phase 2 study (86). Among 24 patients, 12 of whom had cirrhosis, an SVR12 rate of 83% (20 of 24) was observed. There was no difference in response between cirrhotic and noncirrhotic patients (83% [10 of 12] in both groups).

SOF/LDV plus RBV

The single tablet regimen of SOF/LDV has been studied in patients with HCV genotype 3 in the open-label, phase 2, ELECTRON-2 trial conducted in two centres in New Zealand (87). In this study, 51 treatment-naive patients (16% with cirrhosis) were randomly assigned to 12 weeks of SOF/LDV with or without weight-based RBV. Fifty treatment-experienced patients (44% with cirrhosis) all received SOF/LDV plus RBV. Among treatment-naive patients, SVR12 rates were 64% (16 of 25) in the SOF/LDV group and 100% (26 of 26) in those who received SOF/LDV plus RBV. In treatment-experienced patients

TABLE 7
Patients with hepatitis C virus genotype 3

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-naive, cirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 24 weeks*	None	PTV_R/OBV/DSV ± RBV
		SOF/LDV/RBV × 12 weeks		SOF/SIM

**Approved, but clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF (400 mg)/ledipasvir (90 mg) once daily (one tablet)*

treated with SOF/LDV/RBV for 12 weeks, noncirrhotic patients had higher SVR12 rates than those with cirrhosis (89% [25 of 28] versus 73% [16 of 22]). LDV has limited activity against genotype 3 HCV in vitro (88); therefore, although SOF/LDV is a potential therapeutic option in these patients, additional data in diverse populations are necessary before it can be recommended as first-line therapy over other SOF-containing regimens.

Recommendations:

38. In treatment-naive patients and noncirrhotic treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with weight-based RBV for 24 weeks (Class 1, Level B).
39. In cirrhotic, treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPES 4, 5 AND 6 (TABLE 8)

There are limited data to guide treatment decision-making for patients with HCV genotypes 4, 5 or 6 due to the small numbers of patients enrolled in phase 3 clinical trials. In Canada, these genotypes are present in <1% of cases (22). Although the first-generation PIs, BOC and TVR, do not have clinically significant activity against genotypes 4, 5 or 6, SOF (5) and SIM (89) have activity against all of these genotypes. However, due to a paucity of published data, Health Canada and the United States FDA have approved only SOF for the treatment of HCV genotype 4.

PEG-IFN-free regimens

PTV_R/OBV ± RBV: The fixed-dose combination of the ritonavir-boosted, NS3/4A PI PTV_R and the NS5A inhibitor OBV was studied in patients with HCV genotype 4 in the PEARL-I study (90). Treatment-naive patients were randomly assigned to receive PTV_R/OBV with or without weight-based RBV for 12 weeks; all treatment-experienced patients received RBV. Nearly all patients (93%) in this study had mild fibrosis (F0 to F2) and none had cirrhosis. Among subjects who received PTV_R/OBV plus RBV, all treatment-naive (42 of 42) and treatment-experienced patients (41 of 41) achieved an SVR12. However, the SVR12 rate was lower (91% [40 of 44]) among treatment-naive patients randomly assigned to the RBV-free regimen, suggesting that RBV is necessary with this drug combination. The safety profile of PTV_R/OBV plus RBV was similar to that observed in patients with HCV genotype 1 who were also treated with DSV (14,15).

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in patients with HCV genotype 4 in a single-center, open-label phase 2a trial (National Institutes of Allergy and Infectious Diseases SYNERGY) (91). Twenty-one patients (38% treatment-experienced; 40% with cirrhosis) received SOF/LDV for 12 weeks. Among 20 patients who completed the post-treatment follow-up period, 19 (95%) achieved SVR12. No patient discontinued treatment due to an adverse event. In a similar, open-label study conducted among 25 patients with HCV genotype 6 (92% treatment-naive; 8% with cirrhosis; 80% IL28B CC genotype) from two centres (ELECTRON-2) (87), a 12-week regimen of SOF/LDV resulted in an SVR12 rate of 96% (24 of 25). Although in vitro data suggest that SOF/LDV should be efficacious in patients with HCV genotype 5 (88), it cannot currently be recommended in this patient subgroup until clinical trial data are available.

SOF and RBV: The all-oral combination of SOF (400 mg daily) and weight-based RBV for 12 or 24 weeks was studied in a randomized trial conducted among 103 Egyptian patients with HCV genotype 4 (52% treatment-experienced; 17% with compensated cirrhosis) (92). Among treatment-naive subjects, the SVR12 rates in the 12- and 24-week treatment arms were similar (84% [21 of 25] versus 92% [22 of 24]). Whereas noncirrhotic patients had similar responses in the 12- and 24-week treatment arms (86% [19 of 22] versus 90% [19 of 21]), patients with cirrhosis appeared to benefit from prolonged therapy (SVR12 in 12- versus 24-week arms: 67% [two of three] versus 100% [three of three]); however, the sample size was limited. Among treatment-experienced patients (41% nonresponders), a 24-week regimen was superior overall (SVR12 rates in 12- versus 24-week arms: 70% [19 of 27] versus 89% [24 of 27]) and in noncirrhotic patients (73% [16 of 22] versus 95% [20 of 21]). In patients with cirrhosis, SVR12 rates in the 12- and 24-week treatment groups were 60% (three of five) and 67% (four of six), respectively (92). These results were supported by a small trial of Egyptian persons living in the United States treated with SOF and weight-based RBV for 12 or 24 weeks (93). In treatment-naive patients, the SVR12 rate was 79% (11 of 14) in patients treated for 12 weeks and 100% (14 of 14) in those treated for 24 weeks. In treatment-experienced patients, corresponding SVR12 rates were 59% (10 of 17) and 87% (13 of 15).

PEG-IFN-containing regimens

SOF, PEG-IFN and RBV: In the phase 2 ATOMIC study (94), SOF (400 mg once daily) was administered for 24 weeks in combination with PEG-IFN/RBV to a small number of patients with HCV genotypes 4 and 6. SVR12 rates of 82% (nine of 11) in patients with genotype 4 and 100% (five of five) in genotype 6 were observed, supporting the antiviral activity of this regimen. In the phase 3 NEUTRINO study (5), a small subset of patients with HCV genotypes 4 (n=28), 5 (n=1) and 6 (n=5) received this regimen for a shorter 12-week treatment period, and SVR12 rates of 96% (27 of 28) in patients with genotype 4 and 100% (six of six) for genotypes 5 and 6 were reported. The one patient with genotype 4 who failed to achieve an SVR12 had cirrhosis and relapsed after cessation of therapy. The tolerability was similar to that observed historically among patients treated with PEG-IFN and RBV.

SIM, PEG-IFN and RBV: The RESTORE study was a phase 3, single-arm, open-label trial that evaluated SIM with PEG-IFN/RBV in 35 treatment-naive and 72 treatment-experienced patients with HCV genotype 4 (95). All patients received 12 weeks of triple therapy followed by 12 or 36 weeks of PEG-IFN and RBV dual therapy. Treatment-naive and relapser patients were eligible for RGT (an additional 12 weeks of PEG-IFN and RBV dual therapy if HCV RNA <25 IU/mL at week 4 and undetectable at week 12; otherwise, an additional 36 weeks) while partial and null responders received 36 weeks of dual therapy (48 weeks total). Overall, 65% (70 of 107) of patients achieved SVR12 (83% [29 of 35] of treatment-naive patients, 86% [19 of 22] of relapsers, 60% [six of 10] of partial responders and 40% [16 of 40] of null responders). The majority of patients (89% of treatment-naive and 91% of relapsers) met criteria for shortened therapy and SVR12 rates of 94% and 95% were observed in these groups, respectively. Safety was similar to that observed in other phase 3 trials of SIM/PEG-IFN/RBV therapy (6,7).

Recommendations:

40. Patients with HCV genotype 4 should be treated with coformulated PTV_R/OBV plus weight-based RBV or SOF/LDV alone for 12 weeks (Class 1, Level B).
41. Patients with HCV genotype 5 should be treated with SOF (400 mg daily) and PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).
42. Patients with HCV genotype 6 should be treated with SOF/LDV for 12 weeks (Class 1, Level B).

ANTIVIRAL RESISTANCE

Emergence of RAVs must be considered with all DAA-based therapies. Due to the high replication rate of HCV and the low fidelity of its RNA-dependent RNA polymerase, new variants emerge continuously (96-98). HCV circulates as a large of population of related viruses known as quasispecies. Variants with mutations that lead to DAA resistance emerge by chance and are present at low frequencies

TABLE 8
Patients with hepatitis C virus (HCV) genotypes 4, 5 and 6

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 4	PTV_R/OBV/RBV × 12 weeks	SOF/RBV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	SOF/LDV × 12 weeks		SIM/PEG/RBV × 24-48 weeks*	PEG/RBV/BOC or TVR
Genotype 5	SOF/PEG/RBV × 12 weeks	None	None	PTV_R/OBV/DSV ± RBV
Genotype 6	SOF/LDV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	

**Treatment-naive and previous relapser patients with HCV genotype 4 should be treated for 24 weeks total (12 weeks of simeprevir/ peginterferon alfa-2a or peginterferon alfa-2b/ribavirin [SIM/PEG/RBV] followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial and null responders with HCV genotype 4 should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV: weight-based dosing (1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF(400 mg)/ledipasvir (90 mg) once daily (one tablet); TVR telaprevir*

before DAA exposure. With DAA exposure, these resistant variants have a selective advantage over wild-type virus and will emerge as the dominant strains in the quasispecies. The probability that resistance will emerge with particular DAAs depends on their genetic barrier to resistance. This barrier usually reflects the number of nucleotide substitutions that must occur for high-level resistance to emerge. For example, the common PI mutation, R155K, requires two substitutions in a genotype 1b virus, but a single substitution in a genotype 1a virus and, consequently, this variant is much more common in patients with genotype 1a (99). In addition to the genetic barrier, the fitness of the RAV is important. A RAV that replicates very poorly is unlikely to emerge on therapy and will be quickly suppressed by wild-type virus once selective drug pressure is removed (97,98). For example, the S282T variant that confers resistance to SOF has extremely low replicative fitness and, as a result, has been identified only rarely in patients during SOF therapy and quickly disappears on treatment cessation (100). In contrast, many variants resistant to NS5A inhibitors are very fit and compete well with wild-type virus (88,101). As a result, NS5A-resistant variants are found in 10% to 15% of genotype 1 patients before drug exposure and persist long after therapy is discontinued in patients who fail an NS5A inhibitor-containing regimen (8,9).

Strategies to overcome resistance include avoiding DAA monotherapy and DAA dose reductions, maximizing adherence, combining DAAs with nonoverlapping resistance profiles, choosing DAAs with high barriers to resistance, and combining DAAs with PEG-IFN and RBV (96). NS5A inhibitors (eg, LDV, OBV), non-nucleoside polymerase inhibitors (eg, DSV) and NS3/4A PIs (eg, TVR, BOC, SIM) have low barriers to resistance (88). However, when potent agents of multiple classes are combined, on-treatment virological failure is extremely rare (eg, one patient of 473 treated with PTV_R/OBV/DSV plus RBV in the SAPPHIRE-I trial) and post-treatment relapse is very uncommon (eg, seven of 463 patients in this trial) (15). However, resistance to two or all three classes of drugs has been identified in almost all patients with virological failure on this combination. LDV-resistant variants are also uncommon, but present at the time of relapse in most patients who fail SOF/LDV combination therapy (8,9).

There are no data to support pretreatment resistance testing. In patients who have failed a DAA-containing regimen, it is reasonable to assume that resistance to that DAA is present at the time of retreatment. Therefore, a regimen containing DAAs without overlapping resistance should be selected in this situation. For example, in patients who have failed TVR or BOC, SOF/LDV combination therapy is very effective. In the ION-2 trial (9), 159 of 163 patients (98%) with persistent PI resistance at treatment initiation achieved an SVR12 with this regimen. Although RAVs may return to pretreatment levels after prolonged duration off therapy, there are no data on treating patients with PI resistance with a PI-containing regimen (eg, PTV_R/OBV/DSV). Therefore, this approach should not be adopted, particularly given the presence of other proven alternatives (ie, SOF/LDV).

NS5A resistance is of slightly more concern because NS5A inhibitors are a component of most all-oral regimens (88). In patients with baseline NS5A resistance, 90% achieved SVR12 with SOF/LDV in the ION-1 (8) and ION-3 (10) trials. Although this SVR rate was slightly lower than in patients without baseline resistance, the differences were not statistically significant and, therefore, pretreatment identification of resistance would not change management. Detailed baseline sequencing was not performed on all patients treated with the PTV_R/OBV/DSV regimen in the phase 3 trials (13-15,75,83); however, the rates of virological failure were low, suggesting that baseline NS5A resistance is unlikely to be a major issue. Whether retreatment of patients with emergent NS5A resistance with an NS5A-inhibitor-containing regimen will be effective remains to be determined.

Recommendations:

43. DAAs should not be used as monotherapy (Class 1, Level B).
44. Dosage reductions of DAAs should not be used to manage treatment-related side effects (Class 2a, Level C).
45. Adherence with DAAs should be maximized to reduce the likelihood of resistance (Class 2a, Level C).
46. Patients who failed therapy with a PI in the past should be treated with a regimen that does not contain a PI (Class 1, Level B).
47. With the exception of testing for Q80K in patients being considered for treatment with SIM, PEG-IFN and RBV, there is no role for baseline resistance testing with current DAA regimens (Class 1, Level A).

DDIs

Before the initiation of any DAA, potential DDIs must be considered, including those attributable to prescription and over-the-counter pharmaceuticals and herbal preparations. Identification of potential interactions requires knowledge of the metabolism of these agents. All currently available HCV PIs (TVR, BOC, SIM, PTV) are inhibitors and substrates of Cytochrome P450 3A4 (CYP3A4). Ritonavir, which is used to increase exposure and allow for once-daily dosing of PTV, is also an inhibitor and substrate of CYP3A4. Therefore, PIs are contraindicated with medications that are potent inducers of CYP3A4/5, which would reduce plasma concentrations and the therapeutic effect of the PI, and for those highly dependent on CYP3A4/5 for clearance, in which elevated plasma concentrations are associated with serious and/or life-threatening events (ie, a narrow therapeutic index). Other drug-metabolizing pathways are involved in individual PI handling that may affect DDIs. NS5A inhibitors and nucleotide polymerase inhibitors have fewer known DDIs than PIs; however, before starting therapy, all concomitant medications should be reviewed. Reference to an online updated database of DDIs is recommended before starting therapy (eg, http://www.hep-druginteractions.org).

Recommendation:

48. All prescription, over-the-counter and herbal medications should be reviewed for possible interactions with DAAs before starting therapy (Class 1, Level C).

FUTURE THERAPEUTIC OPTIONS

Numerous additional antiviral agents are under investigation in various stages of clinical development, from phase 1 though premarketing approval. Promising DAAs include NS3/4A PIs (eg, asunaprevir, grazoprevir, sovaprevir, vedroprevir), NS5A inhibitors (eg, daclatasvir, GS-5816, elbasvir, ACH-3102 and samatasvir), and non-nucleoside (eg, beclabuvir and GS-9669) and nucleotide NS5B polymerase inhibitors (eg, MK-3682 and ACH-3422). As new data regarding these agents emerge, including their receipt of regulatory approval, these HCV management guidelines will be updated.

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REFERENCES

1. Shiffman RN, Shekelle P, Overhage JM, et al. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003;139:493-8.
2. American Heart Association. <http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf> (Accessed February 1, 2012).
3. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol 2012;26:359-75.
4. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-44.
5. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
6. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014;384:414-26.
7. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): A phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014;384:403-13.
8. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98.
9. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
10. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-88.
11. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867-77.
12. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
13. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
14. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14.
15. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
16. Hull M, Shafran S, Tseng A, et al. CIHR Canadian HIV Trials Network Co-Infection and Concurrent Diseases Core: Updated Canadian adult guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfected patients. Can J Infect Dis Med Microbiol 2014;25:311-20.
17. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: A Canadian population-based study of hospitalizations from 1994 to 2004. Can J Gastroenterol 2008;22:381-7.
18. Myers RP, Krajden M, Bilodeau M, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol 2014;28:243-50.
19. Schanzer DL, Paquette D, Lix LM. Historical trends and projected hospital admissions for chronic hepatitis C infection in Canada: A birth cohort analysis. CMAJ 2014;Open 2:E139-144.
20. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Rep 2013;24:3-13.
21. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007. Final Report. <http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf>. (Accessed February 1, 2012).
22. Antonishyn NA, Ast VM, McDonald RR, et al. Rapid genotyping of hepatitis C virus by primer-specific extension analysis. J Clin Microbiol 2005;43:5158-63.
23. Shah HA, Heathcote J, Feld JJ. A Canadian screening program for hepatitis C: Is now the time? CMAJ 2013;185:1325-8.
24. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. Clin Infect Dis 2011;52:889-900.
25. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology 2014 [Epub ahead of print].
26. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology 2008;135:821-9.
27. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010;139:1593-601.
28. Myers RP, Cooper C, Sherman M, et al. Outcomes of chronic hepatitis C therapy in patients treated in community versus academic centres in Canada: Final results of APPROACH (a prospective study of peginterferon alfa-2a and ribavirin at academic and community centres in Canada). Can J Gastroenterol 2011;25:503-10.
29. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis 1999;(19 Suppl 1):77-85.
30. Cacoub P, Ratziu V, Myers RP, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. J Hepatol 2002;36:812-8.
31. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-13.
32. Poynard T, McHutchison J, Davis GL, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. Hepatology 2000;32:1131-7.

33. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-93.
34. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-84.
35. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509-516, e501.
36. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8, e281.
37. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.
38. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-24.
39. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.
40. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.
41. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-17.
42. MacParland SA, Bilodeau M, Grebely J, et al. The 3rd Canadian Symposium on Hepatitis C Virus: Expanding care in the interferon-free era. Can J Gastroenterol Hepatol 2014;28:481-7.
43. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15-20.
44. Hellard M, Rolls DA, Sacks-Davis R, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. Hepatology 2014;60:1861-70.
45. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
46. Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology 2007;132:1767-77.
47. Sherman KE, Sulkowski MS, Zoulim F, et al. Follow-up of SVR durability and viral resistance in patients with chronic hepatitis C treated with telaprevir-based regimens: Interim analysis of the EXTEND study (Abstract 248). Hepatology 2011;54(Suppl 4):485A.
48. Bedossa P. Liver biopsy. Gastroenterol Clin Biol 2008;32:4-7.
49. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: A population-based study including 4275 biopsies. Liver Int 2008;28:705-12.
50. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017-44.
51. Guha IN, Myers RP, Patel K, Talwalkar JA. Biomarkers of liver fibrosis: What lies beneath the receiver operating characteristic curve? Hepatology 2011;54:1454-62.
52. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: A systematic review. Hepatology 2007;46:912-21.
53. Poynard T, Imbert-Bismut F, Munteanu M, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. Comp Hepatol 2004;3:8.
54. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. Gastroenterology 2008;134:960-974.
55. Myers RP, Elkashab M, Ma M, Crotty P, Pomier-Layrargues G. Transient elastography for the noninvasive assessment of liver fibrosis: A multicentre Canadian study. Can J Gastroenterol 24:661-70.
56. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology 2012;55:199-208.
57. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300-14.
58. Venkatesh SK, Ehman RL. Magnetic resonance elastography of liver. Magn Reson Imaging Clin N Am 2014;22:433-46.
59. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: A pilot study. Hepatology 2012;56:2125-33.
60. Sebastiani G, Ghali P, Wong P, et al. Physicians' practices for diagnosing liver fibrosis in chronic liver diseases: A nationwide Canadian survey. Can J Gastroenterol Hepatol 2014;28:23-30.
61. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970-9, e1971-3.
62. Vergniol J, Boursier J, Coutzac C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology 2014;60:65-76.
63. Pang JX, Zimmer S, Niu S, et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. PLoS One 2014;9:e95776.
64. Steadman R, Myers RP, Leggett L, et al. A health technology assessment of transient elastography in adult liver disease. Can J Gastroenterol 2013;27:149-58.
65. Poynard T, Ngo Y, Munteanu M, et al. Biomarkers of liver injury for hepatitis clinical trials: A meta-analysis of longitudinal studies. Antivir Ther 2010;15:617-31.
66. Vergniol J, Foucher J, Castera L, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16:132-40.
67. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798-801.
68. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
69. Kurbanov F, Abdel-Hamid M, Latanich R, et al. Genetic polymorphism in IL28B is associated with spontaneous clearance of hepatitis C virus genotype 4 infection in an Egyptian cohort. J Infect Dis 2011;204:1391-4.
70. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105-9.
71. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41:1100-4.
72. Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nat Genet 2013;45:164-71.
73. Kronenberger B, Zeuzem S. New developments in HCV therapy. J Viral Hepat 2012;19(Suppl 1):48-51.
74. Gilead Sciences Inc. Product Monograph: Harvoni (Ledipasvir/Sofosbuvir) Tablets 90 mg/400 mg Antiviral Agent. <www.gilead.ca/pdf/ca/harvoni_pm_english.pdf>. October 14, 2014. (Accessed November 6, 2014).
75. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-92.
76. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: The COSMOS randomised study. Lancet 2014;384:1756-65.
77. Bae A, Sun SC, Qi X, et al. Susceptibility of treatment-naive hepatitis C virus (HCV) clinical isolates to HCV protease inhibitors. Antimicrob Agents Chemother 2010;54:5288-97.
78. Paolucci S, Fiorina L, Piralla A, et al. Naturally occurring mutations to HCV protease inhibitors in treatment-naive patients. Virol J 2012;9:245.
79. Andonov A, Kadkhoda K, Osiowy C, Kaita K. Pretreatment resistance to hepatitis C virus protease inhibitors boceprevir/telaprevir in hepatitis C virus subgenotype 1a-infected patients from Manitoba. Can J Gastroenterol 2013;27:414-6.
80. Antiviral Drugs Advisory Committee Meeting Briefing Document. Simeprevir (TMC435) Treatment of Patients with Chronic Hepatitis C. NDA 205123. October 24, 2013. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM371624.pdf>. (Accessed November 17, 2014).

81. Bourliere M, Bronowicki JP, De Ledinghen V, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy (Abstract LB-6). Hepatology 2014;60:13-4.
82. Bourliere M, Sulkowski M, Omata M, et al. An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin (Abstract 82). Hepatology 2014;60:239A.
83. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359-65, e351.
84. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. Gastroenterology 2014;146:1669-79, e1663.
85. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology 2014;146:430-41, e436.
86. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatology 2014 [Epub ahead of print].
87. Gane EJ, Hyland RH, An D, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection (Abstract LB-11). Hepatology 2014;60:22.
88. Gao M. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. Curr Opin Virol 2013;3:514-20.
89. Moreno C, Berg T, Tanwandee T, et al. Antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2-6: TMC435-C202, a phase IIa, open-label study. J Hepatol 2012;56:1247-53.
90. Pol S, Reddy KR, Baykal T, et al. Interferon-free regimens of ombitasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results (Abstract 1928). Hepatology 2014;60:1129A.
91. Kapoor R, Kohli A, Sidharthan S, et al. All oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: Interim results from the NIAID SYNERGY Trial (Abstract 240). Hepatology 2014;60:321A.
92. Esmat GE, Shiha G, Omar RF, et al. Sofosbuvir plus ribavirin in the treatment of Egyptian patients with chronic genotype 4 HCV infection (Abstract 959). Hepatology 2014;60:662A-663A.
93. Ruane PJ, Ain D, Stryker R, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. J Hepatol [Epub ahead of print].
94. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): An open-label, randomised, multicentre phase 2 trial. Lancet 2013;381:2100-7.
95. Moreno C, Hezode C, Marcellin P, et al. Once-daily simeprevir (TMC435) with peginterferon/ribavirin in treatment-naive or treatment-experienced chronic HCV genotype 4-infected patients: Final results of a phase III trial (Abstract). J Hepatol 2014;60:S535.
96. Feld JJ. Interferon-free strategies with a nucleoside/nucleotide analogue. Semin Liver Dis 2014;34:37-46.
97. Halfon P, Sarrazin C. Future treatment of chronic hepatitis C with direct acting antivirals: is resistance important? Liver Int 2012;32(Suppl 1):79-87.
98. Vermehren J, Sarrazin C. The role of resistance in HCV treatment. Best Pract Res Clin Gastroenterol 2012;26:487-503.
99. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009;50:1709-18.
100. Svarovskaia ES, Dvory-Sobol H, Parkin N, et al. Infrequent development of resistance in genotype 1-6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials. Clin Infect Dis 2014;59:1666-74.
101. Kohler JJ, Nettles JH, Amblard F, et al. Approaches to hepatitis C treatment and cure using NS5A inhibitors. Infect Drug Resist 2014;7:41-56.

This is Exhibit "C" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta
this 11 day of MARCH 2015.

A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor

CIHR CANADIAN HIV TRIALS NETWORK CO-INFECTION AND CONCURRENT DISEASES CORE

Updated Canadian Adult Guidelines for the Treatment of Hepatitis C infection in HIV/Hepatitis Co-infected patients

October 18 2014 – Re-Submitted Version

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Running Head: Canadian Co-Infection Treatment Guidelines (Updated)

Structured Abstract:

Background: HCV co-infection occurs in 20-30% of Canadians living with HIV and is responsible for a heavy burden of morbidity and mortality. HIV-HCV management is more complex due to the accelerated progression of liver disease, the timing and nature of ARV and HCV therapy, mental health and addictions management, socioeconomic obstacles and drug-drug interactions between new HCV direct acting antiviral (DAA) therapies and ARV regimens.

Purpose: Update national standards for management of HCV-HIV co-infected adults in the Canadian context.

Methods: A standing working group with specific clinical expertise in HIV-HCV co-infection was convened by The Canadian Institute of Health Research HIV Trials Network (CTN) to review recently published HCV antiviral data and update Canadian HIV-HCV Co-Infection Guidelines.

Results: Recent data suggest that the gap in SVR rates between HCV mono-infection and HIV-HCV co-infection has been eliminated with newer HCV antiviral regimens. All HIV-HCV co-infected individuals should be assessed for HCV therapy. First line treatment for genotypes 1-6 includes pegylated interferon and weight-based ribavirin dosing plus the nucleotide sofosbuvir for 12 weeks. Sofosbuvir in combination with the protease inhibitor simeprevir for genotype 1 infection is another first line consideration. Sofosbuvir with ribavirin for 12 weeks (genotype 2) and 24 weeks (genotype 3) is also recommended as first line treatment.

Discussion: Recommendations may not supersede individual clinical judgement.

Keywords: HIV, HCV, Co-infection, Treatment, Antivirals, Updated Guidelines

Introduction

Since the publication of the Canadian Co-infection Guidelines in December 2013(1) there have been substantial developments in the field of hepatitis C (HCV) therapeutic management. In addition to the presentation of new information regarding dosing and duration of currently available agents for HCV therapy, two new additional HCV direct-acting antiviral agents (DAAs) have been licensed for use in Canada and the United States. The availability of these agents (sofosbuvir and simeprevir) has required revised recommendations for therapy in HCV mono-infected individuals.(2) Furthermore, it is anticipated that several interferon-free, oral combination DAA regimens will be approved by Health Canada within the year.(3-5) Here we review current protocols for the treatment of HCV in the setting of HIV co-infection and make recommendations for the use of these newer currently available HCV DAAs. These guidelines will continue to be updated on a regular basis as new agents become available for use.

Current HCV therapy in Genotype 1 co-infected patients

The standard of care for genotype 1 HCV-infected individuals since the latter part of 2011 has comprised of triple therapy with pegylated interferon, ribavirin and a HCV protease inhibitor boceprevir or telaprevir. Published phase III studies with both boceprevir and telaprevir in HCV mono-infected populations demonstrate markedly improved SVR rates compared with dual peginterferon plus ribavirin therapy in treatment naïve, prior relapser, prior partial responder and prior null responder populations.(6-9)

Results from two phase II randomized, comparative studies indicate markedly improved sustained virologic response (SVR) outcomes with these triple-therapy regimens for HCV

genotype 1 treatment naïve patients co-infected with HIV.(10, 11) SVR rates achieved in these studies now approximate those seen in mono-infected patients (63-74%), a significant advance over those seen in pegylated interferon/ribavirin trials.(12)

Telaprevir-based therapy in co-infection

A randomized, double-blind, clinical trial compared pegylated interferon α-2a and ribavirin with or without telaprevir in HIV-seropositive, HCV genotype 1-infected patients not on antiretroviral therapy with CD4 counts above 500 cells/μL (n=13, Part A) and in patients receiving suppressive antiretroviral therapy (n=24, Part B).(10) Overall, 74% of patients receiving telaprevir achieved an SVR compared to 45% of those receiving pegylated interferon and ribavirin. Relapse rates were 3% for those receiving telaprevir vs. 15% in those receiving pegylated interferon and ribavirin. SVR rates were similar between those on ART and those who were not. Serious adverse events were seen in 5% of those receiving 48 weeks of fixed duration pegylated interferon α-2a and ribavirin (the majority received fixed 800 mg ribavirin dosing with a few subjects receiving weight-based dosing). Patients were dosed with either 12 weeks of telaprevir 750 mg q8h or an 1125 mg q8h dose was used for patients on efavirenz due to anticipated drug-drug interactions.

Interim analyses from three additional studies now support the use of telaprevir in treatment-experienced co-infected patients. These trials demonstrate comparable outcomes with a twice daily dose of 1125 mg telaprevir in co-infected patients, which has been previously been shown to be non-inferior to standard q8hr dosing in mono-infected individuals.(13) In addition, they provide supportive evidence for the use of response-

guided therapy in HCV treatment-naïve patients and those with prior relapse. Finally these new data provide evidence for the use of telaprevir in treatment-experienced patients, a population not included in the original co-infection trial.

In the UNITE phase 3 open-label study, 182 participants received telaprevir-based therapy (dosed twice daily); treatment-naïve and prior relapsers receiving response-guided therapy if rapid virologic response on treatment was demonstrated, while those without rapid virologic response (RVR – See Table 1 for definitions) as well as prior partial and null responding patients were offered a fixed 48 week course of therapy.(14) The SVR12 rates obtained were similar to those seen previously, with 67% of naïve individuals, 68% of prior relapsers and 60% of partial responders achieving SVR. SVR rates were lower in prior null responder with only 39% achieving SVR12. Overall, 97% experienced an adverse event during therapy, 13% of which were serious adverse events. In the INSIGHT open-label trial, 164 participants (98 of whom were treatment-experienced, including 51 prior null-responders) received standard telaprevir-based therapy dosed three times daily (q8hr) in a similar response-guided algorithm.(15) Complete early virologic response ($cEVR_{12}$) rates were high, with 80% of naïve individuals, 83% of those prior partial response and 57% of null responders achieving undetectable HCV RNA at week 12 of treatment.(15)

In ANRS HC-26 (n=69, 39% relapsers, 31% prior partial responders/breakthrough and 30% non-cirrhotic null responders) participants received a four week lead-in of pegylated interferon and weight-based ribavirin, 12 weeks of triple therapy with the addition of telaprevir, with an additional course of pegylated interferon and ribavirin for a total of 48 or 72 weeks in a response-guided fashion dependent on results of the week 8 (week 4

triple therapy outcome).(16) Patients were included if they had stable CD4 cell counts > 200 cells/μL (CD4% >15%) with suppressed HIV viral load on efavirenz, atazanavir/ritonavir or raltegravir-based regimens. The METAVIR score was F3 in 16% and 23% were cirrhotic (F4). Sustained virologic response (SVR24 response – see Table 1) was achieved in 80% of individuals and did not appear to be influenced by the fibrosis stage (F1-2 83%, F3-4 78%), or previous response type (with EOT achieved by those with prior relapse 74%, prior breakthrough 83%, partial response 100% and prior null response 71%), although sample size for these sub-groups was small. Grade 4 adverse events occurred in 22% of cases, including anemia (10%) and infections (3%). Dose reduction of pegylated interferon or ribavirin was required in 22% and 43%, respectively.Sixty-five percent of study participants were administered erythopoietin and 23% required blood transfusion during the extended course of therapy.(17)

Boceprevir-based therapy in co-infection

Boceprevir was evaluated in 98 co-infected patients in a placebo-controlled randomized trial.(11) All patients were on antiretroviral therapy with stable, HIV suppression. Antiretroviral regimens allowed in this study consisted of a ritonavir-boosted protease inhibitor, raltegravir, or maraviroc in conjunction with two nucleoside inhibitors other than zidovudine, stavudine or didanosine. Most participants were receiving atazanavir, lopinavir, or darunavir-based regimens. Non-nucleoside reverse transcriptase inhibitor based regimens were not allowed in this protocol. Only 5 of 98 participants were cirrhotic. All participants received 48 weeks of therapy consisting of standard four week lead-in phase with pegylated interferon α-2b and weight-based ribavirin, followed by a fixed duration of 44 weeks of boceprevir 800 mg q8h or placebo. Overall, an SVR24 was

achieved in 63% of triple therapy recipients (n=64) versus 29% of pegylated interferon α-2b and ribavirin treated study participants (n=34).(11) Adverse events were common in those receiving boceprevir (41% vs. 26%). Despite the successful use of HIV protease inhibitors in this trial, subsequent pharmacokinetic studies have suggested potential for significant interactions (See Table 2 – Drug Interactions with HCV DAAs).

In ANRS HC-27, treatment–experienced patients (n=64), received a standard lead-in phase followed by 44 weeks of triple therapy with boceprevir.(18) Individuals with cirrhosis and prior null response to pegylated interferon and ribavirin were excluded. Those without a week 8 RVR completed an additional 24 weeks (total 72 weeks) of pegylated interferon with ribavirin. The overall SVR12 rate was 53%, with SVR rates of 90% in prior relapsers, 61% in those with partial response and 24% in null responders. In this trial there was an apparent difference in outcome based on underlying ART regimen, with a 41% SVR rate in those receiving atazanavir/ritonavir compared to 70% in those receiving raltegravir.(19)

Conclusion

These results demonstrate that response rates for treatment naïve patients is improved with pegylated interferon, ribavirin and an HCV protease inhibitor compared to SVR rates achieved with pegylated interferon/ribavirin alone. SVR rates approximate those seen in mono-infection with reduced SVR rates observed in those with more advanced disease. In addition, the encouraging interim findings suggest that treatment-experienced co-infected patients will achieve SVR outcomes similar to those seen in mono-infected trials, with highest SVR rates in prior relapsers (higher than treatment naïve patients),

intermediate SVR rates in prior partial responders and the lowest SVR rates in prior null responders. Adverse events, particularly anemia, were common but similar in characteristic and rate to that of HCV mono-infected treatment recipients. These results highlight the need for improved therapeutic options for all HCV-infected individuals with advanced disease or prior treatment failure.

Next Generation DAAs: simeprevir and sofosbuvir

Two new DAAs have recently been approved in Canada and the United States for the treatment of HCV; the NS3/4A protease inhibitor simeprevir, and the novel uridine nucleotide NS5B RNA-dependent RNA polymerase inhibitor sofosbuvir. These agents offer marked improvement over current therapies, as they have much improved side effect profiles, fewer drug interactions, reduced pill burden and in the case of sofosbuvir, offer pan-genotypic coverage with the potential for interferon-free based therapy for all genotypes. As such, they have superseded the use of both telaprevir and boceprevir in current treatment recommendations in the United States.(20)

Simeprevir

Simeprevir is a second-wave NS3/4A protease inhibitor, which offers a number of advantages over boceprevir and telaprevir. The recommended dose in adults with genotype 1 infection is 150 mg once daily with food. Food delays the absorption of simeprevir, increasing the time to reach maximum plasma concentration by 1 to 1.5 hours, and increases the exposure of simeprevir by approximately 60%. Simeprevir is available as a 150 mg capsule, allowing for a significant reduction in pill burden compared to its predecessors in this class. Simeprevir is a substrate of CYP3A4, and a

mild inhibitor of intestinal (but not hepatic) CYP3A4, 1A2, P-glycoprotein (P-gp) and Organic anion transporting polypeptides (OATP) 1B1 (20). Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6.(20) Due to these characteristics, simeprevir is primarily the subject, rather than a perpetrator of pharmacokinetic drug-drug interactions. Co-administration of simeprevir with moderate-strong inducers or inhibitors of CYP3A4 is not recommended due to the potential for significant alterations in simeprevir plasma concentrations. Clinically, this restricts antiretroviral choices for HIV/HCV co-infected patients, as regimens including ritonavir or cobicistat as a booster or the NNRTIs efavirenz, etravirine and nevirapine should not be used [Table 2,3]. Similarly, other inducing/inhibiting agents such as anticonvulsants, rifamycins, dexamethasone, azole antifungals and macrolides should be avoided with simeprevir. In the transplant population, simeprevir may be preferred over telaprevir or boceprevir due to the absence of drug interactions with tacrolimus and cyclosporine.(21)

Use of simeprevir in conjunction with pegylated interferon and ribavirin has been shown to achieve similar improvement in SVR rates in phase II studies, in both naïve and experienced HCV mono-infected patients.(22, 23) Simeprevir used in a response-guided protocol has been assessed in three large phase III clinical trials in HCV monoinfected treatment naïve individuals (QUEST-1, QUEST-2) and prior relapsers (PROMISE).(24-26) In these trials, simeprevir 150 mg daily for the initial 12 weeks of triple therapy with response-guided pegylated interferon/ribavirin for 24 or 48 weeks resulted in SVR12 rates of 80-81% in naïve individuals compared to 50% for those receiving pegylated interferon/ribavirin alone. Overall, amongst naïve individuals, the majority (80% in QUEST-1 and 91% in QUEST-2) met criteria for response-guided therapy (i.e. 24 weeks

total), based on a HCV PCR <25 IU/mL at week 4 with undetectable HCV RNA at week 12. Response rates amongst those who met these criteria were high at 86-91%. Prior relapsers showed similar benefit with 79% of those treated with simeprevir achieving SVR12 compared to 37% in the control arm.(26) The majority of individuals (92.7%) were eligible for response-guided therapy and of those 83% achieved SVR12.

Data in treatment-experienced HCV mono-infected patients is derived from the Phase 2 ASPIRE trial(23) wherein those individuals who received 48 weeks of pegylated interferon and ribavirin had SVR24 rates of 88% in prior relapsers, 86% in prior non-responders and 58% in prior null responders. Recently, the results of the phase 3 ATTAIN trial, the only head-to-head randomized trial of two HCV protease inhibitors, showed comparable SVR rates with 12 weeks of simeprevir vs. 12 weeks of telaprevir, each given with 48 weeks of pegylated interferon alfa-2a for 48 weeks in patients with HCV genotype 1 infection who were partial or null responders to prior dual therapy with peginterferon plus ribavirin.(27) Specifically, SVR12 rates were 70% and 44% in partial and null responders, respectively, treated with simeprevir versus 69% and 46%, respectively, in those treated with telaprevir. There was a lower incidence of anemia and fewer discontinuations for adverse events in simeprevir recipients.

The side effect profile for individuals receiving simeprevir was similar to those on pegylated interferon and ribavirin, with no significant additional toxicities identified. A naturally occurring HCV NS3 polymorphism – the Q80K mutation was associated with reduced SVR rates in genotype 1a patients. This polymorphism occurs in about 45% of North Americans with genotype 1a(28) but only ~18% of Europeans.(29) In the QUEST-1 study those with this mutation had no better response rate with the addition of

simeprevir compared to those in the pegylated interferon/ribavirin arm.(24) Screening at baseline for this mutation in genotype 1a is recommended.

Data in co-infected patients

Simeprevir has been evaluated in treatment naïve and experienced HIV co-infected patients.(30) In the C212 open-label phase III study, 106 individuals received either response-guided therapy for naïve/relapsers (n=64) or standard 12 weeks of triple therapy followed by 36 weeks of pegylated interferon/ribavirin in treatment-experienced patients or those with underlying cirrhosis. Due to potential drug interactions, ART regimens were limited to raltegravir, maraviroc or rilpivirine, with either tenofovir/emtricitabine or abacavir/lamivudine. Overall SVR12 rates were achieved in 79% of naïve individuals, 87% of prior relapsers, 70% of prior partial responders and 57% of null responders. Response rates were reduced in those with cirrhosis (64%) vs. non-cirrhotics (80%) and side effect profile was similar to what is expected with peginterferon plus ribavirin alone.

Sofosbuvir

Sofosbuvir is a nucleotide pro-drug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate, GS-461203 which is incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Sofosbuvir is available as a 400 mg tablet. The approved dose in adults is 400 mg once daily taken without regard to food. After oral administration, sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007. Sofosbuvir and GS-331007 do not inhibit any CYP450 isoenzymes or UGT1A1. Sofosbuvir is a P-gp substrate and breast cancer resistance protein (BCRP) substrate whereas GS-331007 is not. Sofosbuvir should not be

coadministered with potent P-gp inducers such as rifampin or St. John's wort.(31) Significant interactions have not been demonstrated or are not expected between sofosbuvir and antiretrovirals.

Sofosbuvir has been widely evaluated in HCV mono-infected individuals. In the phase III NEUTRINO study, 291 genotype 1-infected treatment naïve individuals received 12 weeks of triple therapy with sofosbuvir 400 mg daily in conjunction with pegylated interferon and ribavirin.(32) Overall SVR12 rates were achieved in 89% of individuals, with lower rates seen in those with cirrhosis than in those without (80% vs. 92%). Side effects appear to be driven predominantly by the receipt of pegylated interferon/ribavirin, but a control group for definitive comparison was not built into the study design. In addition, use of sofosbuvir with ribavirin alone has been evaluated for interferon-ineligible patients with genotype 1 infection. In a small (n=60) phase II study, sofosbuvir with weight-based ribavirin for 24 weeks achieved an SVR24 rate of 68% in individuals deemed to be interferon-ineligible.(33) A relatively high rate of relapse (54%) was seen in those with more advanced disease. Other small trials (ELECTRON, QUANTUM trials) of this interferon-sparing strategy have found SVR rates ranging from 50%-84%.(34, 35)

Limited data exist for treatment-experienced patients. However, given the response seen in individuals with characteristics that would normally be considered unfavourable for response to pegylated interferon and ribavirin, modelling conducted during the approval of sofosbuvir by the United States Food and Drug Administration (FDA) predicts an approximate 78% response in treatment-experienced patients.(36)

Genotypes 2 and 3 HCV Mono-Infection

Sofosbuvir has also been evaluated for use in genotypes 2 and 3 in an initial large non-inferiority comparison to standard pegylated interferon/ribavirin.(32) In the FISSION trial, 499 treatment naïve individuals were randomized to 12 weeks of therapy with sofosbuvir/ribavirin or 24 weeks of pegylated interferon/ribavirin. Individuals with genotype 2 infection had exceptional SVR rates of 97% with sofosbuvir/ ribavirin vs. 76% with pegylated interferon/ribavirin, while those with genotype 3 achieved similar SVR rates to pegylated interferon/ribavirin (56% vs. 63%). Cirrhosis markedly reduced SVR rates for genotype 3 individuals to approximately 30% in both arms. Similar SVR rates were seen in the POSITRON trial in interferon-ineligible patients.(37) In the phase III VALENCE study, improved SVR rates were seen in genotype 3 treatment naïve individuals who received 24 weeks of sofosbuvir/ribavirin with SVR rates 94%, with the sub-group of cirrhotic patients achieving SVR of 90%.(38)

Sofosbuvir has also been evaluated in treatment-experienced genotype 2 and 3 patients. In the FUSION trial, individuals were randomized to receive 12 or 16 weeks of therapy with sofosbuvir and ribavirin. Those with genotype 2 achieved an SVR rate of 86% after 12 weeks and 94% after 16 weeks. SVR rates were much lower for genotype 3, with an SVR rate of 30% in those receiving 12 weeks vs. 62% in those who received 16 weeks of therapy. (37) In the VALENCE study, treatment-experienced genotype 2 patients experienced similar high rates of response (91%) after 12 weeks of therapy of dual therapy. Treatment-experienced patients with genotype 3 treated with 24 weeks of sofosbuvir and ribavirin achieved an SVR of 87% in those without cirrhosis, and only 60% in those with cirrhosis.(39) In the LONESTAR-2 phase II trial, the addition of

pegylated interferon to a 12 week course of sofosbuvir/ribavirin resulted in SVR rates of 83% for genotype 3, with or without cirrhosis.(40)

Data in HIV-HCV co-infected patients

Sofosbuvir was evaluated in HIV co-infected patients in the phase II Study 1910 trial.(41) In this open-label study, 23 co-infected treatment-naïve individuals received sofosbuvir 400 mg daily in conjunction with pegylated interferon and weight-based ribavirin for 12 weeks. Individuals were predominantly genotype-1 infected, with two individuals with genotype 3, and a single individual with genotype 2 and 4 respectively were also enrolled. The ART regimens included efavirenz, rilpivirine, raltegravir and the boosted protease inhibitors atazanavir and darunavir. Overall, the SVR12 was 91%. Side effects were predominantly those of pegylated interferon and ribavirin.

In the Phase III PHOTON-1 study, three cohorts of co-infected patients (genotype 1 treatment naïve patients n=114, genotype 2 (n=28) and 3 (n= 42) naïve patients, and genotypes 2/3 treatment-experienced patients (n=41) were enrolled to receive either 12 weeks or 24 weeks (genotype 1 and treatment-experienced patients) of sofosbuvir with ribavirin.(42) Individuals could be on a wide range of ART regimens due to the lack of drug interactions, or naïve to ART if baseline CD4 cell count was > 500 cells/mm^3. The majority of those enrolled were on ART, receiving predominantly efavirenz, atazanavir or darunavir-based regimens. The SVR24 rate was 75% for genotype 1 participants, 88% for genotype 2, and 67% for genotype 3 patients. Amongst treatment-experienced patients, SVR24 was attained by 92% of genotype 2 and 88% of genotype 3 individuals.

Overall, the regimen was well tolerated, with more adverse events related to sofosbuvir/ribavirin seen in those receiving a 24-week course of therapy.

DAA combination regimens of currently approved agents

Proof of concept studies of interferon-free and ribavirin-sparing combinations of potent DAA agents have rapidly advanced the potential for simple, potent and well-tolerated therapies for HCV.(43-45) Further evaluation of combination DAA therapy has demonstrated potential therapy in patients with advanced disease, in prior null responders and as salvage therapy in patients previously non-responsive to telaprevir and boceprevir-based therapy.(3, 46, 47) In the COSMOS study, HCV mono-infected, treatment naïve and prior null responders with HCV genotype 1 mono-infection, received once daily simeprevir and sofosbuvir, with or without ribavirin for either 12 or 24 weeks.(46) In the first cohort of 80 null responders with METAVIR F0-F2 disease, SVR12 rates with dual therapy were high at 92-93% after 12 or 24 weeks of therapy, and the addition of ribavirin was not clearly associated with improvement in SVR rates.(48) For the second cohort of 87 naïve and null responders with F3-F4 disease, SVR12 rates were 93% with 12 weeks of therapy and 96% with 24 weeks of therapy.(49) The addition of ribavirin did not increase SVR rates but did result in some cases of anemia.(4) On the basis of the COSMOS data, two phase 3 studies, will evaluate 8 vs. 12 weeks of sofosbuvir plus simeprevir in non cirrhotics (OPTIMIST-1) and 12 weeks in cirrhotics (OPTIMIST-2) in HCV genotype 1 mono-infected treatment naïve patients.(50) Ribavirin will not be included in the phase 3 studies. At present, no data exist for this combination in co-infected individuals.

Future DAA combinations

Interferon-free, combination DAA regimens have been or soon will be approved by regulatory agencies, including Health Canada. We anticipate that the regimens mentioned below will rapidly be identified as first line therapies for HCV. However, as HIV-HCV co-infection specific clinic trials evaluating these new regimens have yet to be published, they have not been included in this current iteration of the CIHR CTN HIV-HCV co-infection guidelines.

The combination of sofosbuvir with a NS5A replication inhibitor is particularly promising. This was first demonstrated in a phase 2 study with the NS5A inhibitor daclatasvir, with SVR rates of 98% in genotype 1, 92% in genotype 2 and 89% in genotype 3.(51) Moreover, the combination of sofosbuvir plus daclatasvir resulted in SVRs in 100% of 41 patients who previously failed triple therapy with peginterferon, ribavirin and either telaprevir or boceprevir.

Very recently, three phase 3 trials of the fixed-dose combination of sofosbuvir with the NS5A inhibitor ledipasvir, with and without ribavirin for 8 or 12 weeks in patients with HCV genotype 1 mono-infection demonstrated SVR rates of 93 to 99%, including boceprevir or telaprevir treatment experienced patients and those with cirrhosis.(4, 52) The addition of ribavirin did not increase SVR rates. A New Drug Application (NDA) for sofosbuvir-ledipasvir was filed with the US FDA on February 10, 2014 and received approval in the United States and Canada in October 2014.(53) The combination of sofosbuvir/ledipasvir for 12 weeks is currently under study in HIV/HCV co-infected patients in the ION-4 protocol.

The combination of 3 DAAs, specifically the NS3 protease inhibitor ABT-450 boosted by the CYP3A4 inhibitor ritonavir, the NS5A inhibitor ombitasvir and the NS5B non nucleoside polymerase inhibitor dasabuvir, with ribavirin given for 12 weeks results in SVR rates of 93 to 99% in HCV genotype-1 mono-infected patients, including treatment experienced patients and those with cirrhosis.(5, 54, 55) It appears that ribavirin can be omitted in genotype 1b, but is needed in genotype 1a.(56) A new drug application (NDA) for this regimen was filed with the FDA on April 22, 2014.(57) This regimen is currently under evaluation in the HCV/HIV co-infected patients (TURQUOISE I study). However, the presence of multiple CYP3A4 metabolized medications, including ritonavir, may limit antiretroviral treatment options in HIV co-infected patients considered for this regimen.

Summary

Taken together, these clinical trial results indicate a significant paradigm shift in the management of HCV mono and co-infection is imminent, pending regulatory approvals and eventual addition to provincial formularies. Recent data suggest that the gap in SVR rates between HCV mono-infection and HIV-HCV co-infection has been eliminated with newer HCV antiviral regimens. The "real-world" uptake and efficacy of these agents in vulnerable populations will be important to assess their impact on the burden of HCV disease and sequelae.(1)

Recommendations for Therapy

1. **Genotype 1 Treatment-Naïve Individuals without Cirrhosis**

First Line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12 weeks of therapy. This combination offers short duration of therapy with high SVR rate with no concerns regarding ART drug interactions, and no additional side effects beyond that of pegylated interferon and ribavirin. (Class 1, Level B) (see Appendix for level of evidence criteria)

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily. This regimen has not been evaluated in co-infection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (i.e. treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available. (Class 1, Level C)

Alternative: Therapy for interferon-eligible patients would consist of response-guided therapy with simeprevir 150 mg daily with pegylated interferon and weight-based ribavirin. (Class 1, Level B)

a) Genotype 1a strains must undergo Q80K polymorphism testing prior to use of this regimen, and an alternative DAA should be chosen if Q80K is present.

b) Response-guided therapy with treatment discontinuation at week 24 can be offered if week 4 RNA < 25 IU/mL is attained, but should not be used in individuals with underlying cirrhosis in whom a full 48 week course of pegylated interferon and ribavirin is advised.

c) Drug interactions with ART must be considered with use of simeprevir.

Alternative: Interferon-ineligible individuals can be considered for 24 weeks of sofosbuvir 400 mg daily and weight-based ribavirin. Given the decreased SVR rates seen with this combination, and limited information in those with cirrhosis, deferral of therapy for future combination DAA regimens should be considered. (Class 1, Level B)

2. Genotype 1 Treatment Naïve Individuals with Cirrhosis

First Line: Sofosbuvir 400 mg daily pegylated interferon and ribavirin for 12 weeks. Patients must not have decompensated cirrhosis to receive interferon. (Class 1 , Level B)

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks. This regimen has not been evaluated in co-infection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (i.e. treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available. (Class 1, Level C)

Alternative: Simeprevir 150 mg daily for 12 weeks with pegylated interferon and ribavirin for 48 weeks (assuming genotype 1a recipient is Q80K negative). (Class 1, Level B)

3. Genotype 1 Treatment-Experienced Patients with Prior Relapse (with or without cirrhosis)

See recommendations for Genotype 1 treatment-naïve individuals with or without cirrhosis as above. Retreatment with pegylated interferon, ribavirin and simeprevir is not

recommended in prior relapsers, partial or null responders to other protease inhibitor (boceprevir,telaprevir)-based regimens. (Class 1, Level B)

4. **Genotype 1 Treatment-Experienced Patients - Prior Non-Responders or Null Responders (with or without cirrhosis)**

First Line: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks (NB-based on HCV mono-infection studies). (Class 1, Level C)

Or

First Line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12-24 weeks. (Class 1, Level C)

Alternative: Simeprevir 150 mg daily for 12 weeks with 48 weeks of pegylated interferon and weight-based ribavirin (except in genotype 1a with Q80K). Response-guided therapy is recommended for non-cirrhotic patients with prior relapse, whereas 48 weeks is recommended in prior partial or null responders, with or without cirrhosis. (Class 1, Level B)

5. **Genotype 2 Treatment Naïve Patient**

First Line: Sofosbuvir 400 mg daily with weight-based ribavirin for 12 weeks. (Class 1, Level B)

6. **Genotype 2 Treatment-Experienced Patient**

First Line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks. (Class 1, Level B)

Alternative: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (Class 1, Level C)

Recommendations for treatment-experienced co-infections are based on expert recommendation, utilizing data from a single trial in co-infection and data from other hard-to-cure mono-infected populations.

7. **Genotype 3 Treatment-Naïve Patient**

First Line: Sofosbuvir 400mg daily with pegylated interferon and ribavirin for 12 weeks, particularly if compensated cirrhosis is present and interferon is not contra-indicated. (Class 1, Level C)

OR

First Line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks if interferon contra-indicated or patient considered interferon-ineligible. (Class 1, Level B)

8. **Genotype 3 Treatment-Experienced Patient**

First Line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (Class 1, Level C)

Alternative: Sofosbuvir 400mg daily with ribavirin for 24 weeks if interferon ineligible or intolerant (Class 1, Level B)

9. **Genotype 4 Treatment-Naive and Experienced**

First Line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (NB- based on HCV mono-infection studies) (Class 1, Level C)

There is currently insufficient data in HIV-HCV co-infection with genotype 4-6 to comment on the efficacy of sofosbuvir-simeprevir. Likewise, there is currently

insufficient data in HIV-HCV co-infection with genotype 5-6 to comment on the efficacy of sofosbuvir with pegylated interferon and ribavirin.

Regimens no longer recommended for first line use:

1. Telaprevir and boceprevir are no longer recommended for first line use given the improved safety and tolerability profiles of the new DAA agents.
2. Pegylated interferon and ribavirin as dual therapy for genotype 2/3 individuals.

Circumstances may exist in which first line regimens are not accessible to patients (e.g. restricted funding). The above second line regimens could be considered as treatment options. However, the patient must be fully aware of the diminished likelihood for cure and/or increased likelihood for adverse events compared to first line regimens.

Timing of initiation of HCV therapy in the era of DAAs

At this time it is unclear whether access to newer agents will be standard across the country, and/or which, if any, additional criteria may be imposed by individual provinces/payers to limit access to DAAs given the anticipated costs of these agents. Recommendations for use of newer DAA agents/combinations is based primarily on a review of the currently available data evaluating efficacy and safety in mono-infected and co-infected patients.

Access to appropriate therapy when clinically indicated has long been recommended in Canada by experts involved in the care of patients living with HCV(58) and we would continue to advocate for such an approach for co-infected patients. The authors recognize that due to potential restrictions to access and reimbursement of newer drugs/regimens

for HCV, clinicians and patients may face difficult decisions regarding therapy. In this situation alternate options may be considered.

a. Deferral of therapy

Individuals with early fibrosis may be able to defer therapy compared to those with more advanced disease, as they have lower risk of medium-term progression of disease. These individuals may be able to wait for future combinations and potentially improved access to interferon-free based combinations. If deferral of therapy is considered, updated staging for fibrosis progression is recommended on an annual basis if access to transient elastography is possible, or every 3 years if liver biopsy is to be performed. The clinician must also consider that for dual therapy with pegylated interferon plus ribavirin and triple therapy with pegylated interferon plus one DAA, SVR rates are highest at early fibrosis stages (<F3) and decrease with advancing disease.

Additional considerations of patient readiness, and consideration of possible onward HCV transmission risk for individuals in a core transmitter group (IDU and certain MSM populations) compared to those without high risk for transmission [e.g. many baby boomers (born between approximately 1945-1970)] may influence a decision to consider delaying therapy.

b. Utilization of non-preferred regimens

For cost/access reasons, it may be necessary to use older therapies for HCV with a higher incidence of adverse effects and lower SVR rates in some patients. In all such cases,

patients should be made aware of the existence of newer improved therapies and given the option of potentially paying for them, if they so choose.

References

1. Hull M, Klein M, Shafran S, Tseng A, Giguere P, Cote P, et al. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults. Can J Infect Dis Med Microbiol. 2013 Winter;24(4):217-38.

2. Recommendations for testing, managing, and treating hepatitis C. [Web Page]: American Association for the Study of Liver Diseases and the Infectious Diseases Society of America; 2014 [cited 2014 April 24]; Available from: http://www.hcvguidelines.org.

3. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014 Feb 8;383(9916):515-23.

4. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.

5. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594-603.

6. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

7. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.

8. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.

9. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

10. Sulkowski MS, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV: A Randomized Trial. Ann Intern Med. 2013 Jul 16;159(2):86-96.

11. Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis. 2013 Jul;13(7):597-605.

12. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004 Jul 29;351(5):438-50.

13. Buti M, Agarwal K, Horsmans Y, Sievert W, Janczewska E, Zeuzem S, et al. Telaprevir twice daily is noninferior to telaprevir every 8 hours for patients with chronic hepatitis C. Gastroenterology. 2014 Mar;146(3):744-53 e3.

14. Hare CD, Sherman K, Talal AH, et al. Simplified Dosing and Response-Guided Therapy Using Telaprevir Combination Treatment for Genotype 1 HCV Treatment-Naïve or -Experienced HIV Co-infected Patients: UNITE Interim Analysis. (Abstract 64). Proceedings and Abstracts of HEP DART 2013; December 8-12; Big Island, HI, USA2013.

15. Montes M, Nelson M, M. G, et al, editors. Telaprevir combination therapy in treatment-naive and experienced patients co-infected with HCV and HIV. (Abstract 38). Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

16. Cotte L, Braun J, Lascoux-Combe C, Vincent C, Pol S, Valentin M, et al., editors. High Early Virologic Response with Telaprevir-Pegylated Interferon-Ribavirin in Treatment-experienced HCV Genotype 1/HIV Co-infected Patients: ANRS HC26 TelapreVIH Study. (Abstract 36). 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3-6; Atlanta, GA.

17. Cotte L, Braun J, Lascoux-Combe C, Vincent C, Valantin M, Sogni P, et al. Telaprevir for HIV/Hepatitis C Virus-Coinfected Patients Failing Treatment With Pegylated Interferon/Ribavirin (ANRS HC26 TelapreVIH): An Open-Label, Single-Arm, Phase 2 Trial. Clin Infect Dis. 2013 Aug 18, 2014.

18. Poizette-Martin I, Bellissant E, Piroth L, et al, editors. W48 Response Rate of Boceprevir-PegIFN-RBV in Treatment-Experienced HIV Coinfected Patients with HCV genotype 1: ANRS-HC27 BocepreVIH Study. (Abstract 1105). Program and Abstracts of the 64th American Association for the Study of Liver Diseases; 2013 November 7-11; Washington, DC.

19. Poizette-Martin I, Bellissant E, Colson P, Renault A, Piroth L, Solas C, et al., editors. Boceprevir for Previously Treated HCV-HIV Coinfected Patients: The ANRS-HC27 BocepreVIH Trial. (Abstract 659LB). Abstracts and Proceedings of the 21st Conference on Retroviruses and Opportunistic Infections (CROI); 2014 March 3 - 6; Boston, MA.

20. Galexos (simeprevir) Product Monograph. Janssen Inc. Toronto, ON2013.

21. Ouwerkerk-Mahadevan S, Simion S, Mortier E, et al, editors. No clinically significant interaction between the investigational HCV protease inhibitor simeprevir (TMC435) and the immunosuppressive agents cyclosporine and tacrolimus. (Abstract 80) Abstracts and Proceedings of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2012 November 9-13; Boston, MA.

22. Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology. 2013 Dec;58(6):1918-29.

23. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-41 e6.

24. Jacobson IM, Dore GJ, Foster GR, al. E, editors. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naive patients: results from QUEST-1, a phase III trial. (Abstract 1425). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

25. Manns M, Marcellin P, Poordad F, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naive patients: results from QUEST-2, a phase III trial. (Abstract 1413). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28; Amsterdam, The Netherlands2013.

26. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial. Gastroenterology. 2014 Jun;146(7):1669-79 e3.

27. Reddy KR, Zeuzem S, Zoulim F, et al, editors. A Phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study. Proceedings and Abstracts of the Asian Pacific Association of the Study of the Liver; 2014 March 12-14; Brisbane, Australia.

28. Andonov A, Kadkhoda K, Osiowy C, Kaita K. Pretreatment resistance to hepatitis C virus protease inhibitors boceprevir/telaprevir in hepatitis C virus subgenotype 1a-infected patients from Manitoba. Can J Gastroenterol. 2013 Jul;27(7):414-6.

29. Vicenti I, Rosi A, Saladini F, Meini G, Pippi F, Rossetti B, et al. Naturally occurring hepatitis C virus (HCV) NS3/4A protease inhibitor resistance-related mutations in HCV genotype 1-infected subjects in Italy. J Antimicrob Chemother. 2012 Apr;67(4):984-7.

30. Dieterich D, rockstroh J, Orkin C, Gutierrez F, Klein M, Reynes J, et al. Simeprevir (TMC435) with Peginterferon/Ribavirin in Patients Coinfected with HCV Genotype-1 and HIV-1: A Phase III Study. Clin Infec Dis [serial on the Internet]. 2014; (pii).

31. SOVALDI Product Monograph. Gilead Sciences Canada, Inc. Mississauga, ON2013.

32. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

33. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. Jama. 2013 Aug 28;310(8):804-11.

34. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):34-44.

35. Lalezari J, Nelson D, Hyland RH, et al, editors. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. (Abstract 845). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

36. Muir A, Nelson D, Gordon S, et al, editors. Modeling predicts clinically meaningful SVR rates in genotype 1 treatment-experienced patients based on results in genotype 1 treatment-naive patients treated with sofosbuvir+ peginterferon+ ribavirin for 12 weeks. (Abstract P1220). Abstracts and Proceedings of the 49th European Association for the Study of the Liver meeting; 2014 April 9-13; London, UK.

37. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77.

38. Zeuzem S, Dushelko GM, Salupere R, et al, editors. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. (Abstract 1085) Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

39. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014 May 22;370(21):1993-2001.

40. Lawitz E, Poordad F, Brainard D, et al, editors. Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study. (Abstract LB4) Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

41. Rodriguez-Torres M, Rodriguez-Orengo J, Gaggar A, et al, editors. Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1–4 HCV-Infected Patients Who Are Coinfected With HIV. (Abstract 714). Abstracts and Proceedings of IDWeek; 2013 October 2-6; San Francisco, CA.

42. Sulkowski M, Naggie S, Lalezari J, Fessel W, Mounzer K, Shuhart M, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA. 2014 July 23-30, 2014;312(4):353-61.

43. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012 Jan 19;366(3):216-24.

44. Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):45-53.

45. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Mullhaupt B, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med. 2013 Aug 15;369(7):630-9.

46. Jacobson IM, Ghalib R, Rodriguez-Torres M, et al, editors. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. (Abstract LB3). Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

47. Sulkowski M, Gardiner DF, Rodriguez-Torres M, et al, editors. Sustained virologic response with daclatasvir plus sofosbuvir ± ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or

boceprevir (BOC). (Abstract 1417). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

48. Sulkowski M, Jacobson IM, Ghalib R, et al, editors. Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0-2: COSMOS study subgroup analysis. (Abstract 07). Abstracts and Proceedings of the 49th Annual Meeting of the European Association for the Study of the Liver; 2014 April 9-13; London, UK.

49. Lawitz E, Ghalib R, Rodriguez-Torres M, et al, editors. Simeprevir plus sofosbuvir with/without ribavirin in HCVgenotype 1 prior null-responder/treatment-naive patients (COSMOS study): primary endpoint (SVR12) results in patients with Metavir F3-4 (Cohort 2). (Abstract O165). Abstracts and Proceedings of the 49th Annual Meeting of the European Association for the Study of the Liver; 2014 April 9-13; London, UK.

50. Janssen Initiates Phase 3 OPTIMIST Trials of Once-Daily Simeprevir in Combination with Once-Daily Sofosbuvir for the Treatment of Genotype 1 Chronic Hepatitis C [PDF]: Janssen Pharmaceutical Companies; [updated April 2, 2014; cited 2014 May 30]; Available from: http://www.janssenrnd.com/sites/default/files/pdf/OPTIMIST-Press_Release_FINAL_4%201_14_v3_clean.pdf#zoom=125.

51. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.

52. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med. 2014(370):1879-88.

53. Gilead Files for U.S. Approval of Ledipasvir/Sofosbuvir Fixed-Dose Combination Tablet for Genotype 1 Hepatitis C. [Web Page]: Gilead Sciences, Inc.; [updated February 10, 2014; cited 2014 May 30]; Available from: http://www.gilead.com/news/press-releases/2014/2/gilead-files-for-us-approval-of-ledipasvirsofosbuvir-fixeddose-combination-tablet-for-genotype-1-hepatitis-c.

54. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. N Engl J Med. 2014 Apr 10.

55. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med. 2014 Apr 11.

56. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-Ombitasvir and Dasabuvir with or without Ribavirin for HCV. N Engl J Med. 2014 May 4.

57. AbbVie Submits New Drug Application to U.S. FDA for its Investigational, All-Oral, Interferon-Free Therapy for the Treatment of Hepatitis C. [Web Page]: AbbVie; [updated April 22, 2014; cited 2014 May 30]; Available from: http://abbvie.mediaroom.com/2014-04-22-AbbVie-Submits-New-Drug-Application-to-U-S-FDA-for-its-Investigational-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Hepatitis-C.

58. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol. 2012 Jun;26(6):359-75.

59. Johnson M, Borland J, Chen S, Song I, Savina P, Wynne B, et al., editors. The effect of boceprevir and telaprevir on dolutegravir pharmacokinetics, in healthy adult subjects. (Abstract O-16). Program and Abstracts of the 14th International Workshop on Clinical Pharmacology of HIV Therapy; 2013 April 22-24; Amsterdam, The Netherlands.

60. ViiV Healthcare ULC. Tivicay (dolutegravir) Prescribing Information. Research Triangle Park, NC2013.

61. Custodio J, Guo S, Lawson EB, Cao H, Silva A, Kearney BP, et al., editors. Lack of clinically relevant drug Interactions between elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and telaprevir. (Abstract A-1576). 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2013 September 10-13; Denver, CO.

62. Ouwerkerk-Mahadevan S, Simion A, Peeters M, Beumont-Mauviel M, editors. Summary of pharmacokinetic drug-drug interactions for simeprevir (TMC435), a hepatitis C virus NS3/4A protease inhibitor. (Abstract PE 10/7). Program and Abstracts of the 14th European AIDS Conference (EACS); 2013 October 16-19; Brussels, Belgium.

63. de Kanter C, Blonk M, Colbers A, Schouwenberg B, Burger D. Lack of a clinically significant drug-drug interaction in healthy volunteers between the hepatitis C virus protease inhibitor boceprevir and the HIV integrase inhibitor raltegravir. Clin Infec Dis. 2013;56(2):300-6.

64. Van Heeswijk R, Garg V, Boogaerts G, Vandebosch A, Vandevoorde A, Witek J, et al., editors. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. (Abstract A1-1738a). Abstracts and Proceedings of the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2011 September 17-20; Chicago, IL.

65. Ouwerkerk-Mahadevan S, Sekar V, Peeters M, Beumont-Mauviel M, editors. The pharmokinetic interactions of HCV protease inhibitor TMC435 with rilpivirine, tenofovir, efavirenz or raltegravir in healthy volunteers. (Abstract 49). Program and Abstracts of the 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5-8; Seattle, WA.

66. Kirby B, Mathias A, Rossi S, Moyer C, Shen G, Kearney BP, editors. No clinically significant pharmacokinetic interactions between sofosbuvir (GS-7977) and HIV antiretrovirals Atripla, rilpivirine, darunavir/ritonavir, or raltegravir in

healthy volunteers. (Abstract 1877). Program and Abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2012 November 9-13; Boston, MA.

67. Kasserra C, Hughes E, Treitel M, Gupta S, O'Mara E, editors. Clinical pharmacology of boceprevir: metabolism, excretion, and drug-drug interactions. (Abstract 118). Program and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections; 2011 Feb 27-Mar 2; Boston, MA.

68. Merck Canada Inc. Victrelis (boceprevir) Product Monograph. Kirkland, QC2013.

69. Garg V, Chandorkar G, Yang Y, Adda N, McNair L, Alves K, et al., editors. The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir [abstract PK_13]. Program and Abstracts of the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy; 2011 June 22-23; Cambridge, MA.

70. Van Heeswijk R, Vandevoorde A, Boogaerts G, Vangeneugden T, De Paepe E, Polo R, et al., editors. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers. (Abstract 119). Abstracts and Proceedings of the18th Conference on Retroviruses and Opportunistic Infections; 2011 Feb 27-Mar 2; Boston, MA.

71. Hammond K, Wolfe P, Burton J, Predhomme J, Ellis C, Ray M, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. J Acq Immune Def Syndr. 2013;62(1):67-73.

72. Kakuda TN, Leopold L, Nijs S, Vandevoorde A, Crauwels HM, Bertelsen K, et al., editors. Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir: a randomised, two-way crossover trial. (Abstract O-18). Program and Abstracts of the 13th International Workshop on Clinical Pharmacology of HIV Therapy; 2012 April 16-18; Barcelona, Spain.

73. Rhee E, Feng H-P, Xuan F, Lin WH, Smith C, Zhu Y, et al., editors. Absence of a significant pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and HIV-1 NNRTI rilpivirine. (Abstract 537). Abstracts and Proceedings of the 20th Conference on Retroviruses and Opportunistic Infections (CROI); 2013 March 3-6; Atlanta, GA.

74. Hulskotte EGJ, Feng H-P, Xuan F, van Zutven M, Treitel M, Hughes E, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infec Dis. 2013;56(5):718-26.

75. Vertex Pharmaceuticals Inc. Incivek (telaprevir) Product Monograph. Laval, QC2013.

76. AbbVie Corporation. Kaletra (lopinavir/ritonavir) Prescribing Information. Saint Laurent, Canada2012.

77. Vourvahis M, Plotka A, Kantaridis C, Fang A, Heera J. The effects of boceprevir and telaprevir on the pharmacokinetics of maraviroc: An open-label, fixed-

sequence study in healthy volunteers. J Acquir Immune Defic Syndr. 2014;65(5):564-70.

78. Martel D, Sheehan N, Tremblay C, Turgeon J, Tseng A, Phaneuf D, et al., editors. Pharmacokinetic interaction of the directly acting antiviral agent boceprevir and maraviroc in healthy volunteers. (Abstract P-04). Program and Abstracts of the 14th International Workshop on Clinical Pharmacology of HIV Therapy; 2013 April 22-24; Amsterdam, The Netherlands.

79. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med. 2003 Sep 16;139(6):493-8.

80. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct;54(4):1433-44.

Table 1. Virologic response definitions while on HCV therapy

Definition	Time Point	HCV RNA level	Comment
RVR	Week 4	Undetectable	High positive predictive value for SVR
EVR	Week 12	Undetectable: *Complete EVR* Detectable: *Partial EVR* $\geq$2 $\log_{10}$ drop from baseline Detectable: *Null Responder* <2 $\log_{10}$ drop from baseline	Lack of EVR has very high (>98%) negative predictive value for SVR.
eRVR	Week 4, 12	Undetectable	High positive predictive value for SVR with telaprevir-and simeprevir based triple therapy
Partial Response	Week 12+	Partial EVR at week 12 with no subsequent negative HCV RNA test	Treatment failure (pEVR + week 24 HCV RNA detectable, has 100% NPV for SVR)
EOT Response	treatment completion (number of weeks, varies by regimen)	Undetectable	
Relapser	any time after EOT (usually checked 12 or 24 weeks after EOT)	Undetectable at EOT, Detectable after EOT	Treatment Failure (relapse > 12 weeks after EOT suggests possibility of re-infection; viral sequencing should be considered)
SVR 12	Week 60	Undetectable	Predicts SVR24 in mono-infected patients
SVR 24	Week 72	Undetectable	Treatment Success

RVR: rapid virologic response; SVR: sustained virologic response; EVR: early virologic response; eRVR: extended rapid virologic response; pEVR: partial early virologic response; NPV: negative predictive value ; EOT: end of treatment

Table 2. Drug-drug interactions between antiretroviral agents and directly acting antivirals for hepatitis C

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
Dose	800 mg q8h with food	1125mg q12h with food (not low fat)	150 mg daily with food	400 mg daily
Integrase Inhibitors				
Dolutegravir	No clinically significant changes in either drug. No dose adjustment required(59, 60)	No clinically significant changes in either drug. No dose adjustment required.(59, 60)	Co-administration has not been studied but no expected clinically significant drug interaction	Co-administration has not been studied but no expected clinically significant drug interaction
Elvitegravir/ cobicistat	Co-administration has not been studied but co-administration could potentially lead to reduced drug concentrations of both boceprevir and elvitegravir/cobicistat	No clinically significant changes in either drug. No dose adjustment required.(61)	Not recommended with cobicistat-boosted regimens due to risk of significantly increased simeprevir concentrations.(20, 62)	Co-administration has not been studied but no expected clinically significant drug interaction
Raltegravir	No clinically significant changes in either drug. No dose adjustment required.(63)	No clinically significant changes in either drug. No dose adjustment required.(64)	No clinically significant changes in either drug. No dose adjustment required.(65)	No clinically significant changes in either drug. No dose adjustment required.(20, 66)
Non-Nucleoside Reverse Transcriptase Inhibitors				
Efavirenz	44% ↓ Cmin, 19% ↓ AUC of boceprevir. Avoid combination.(67, 68)	47% ↓ Cmin of telaprevir; ↑ telaprevir dose to 1125 mg q8h with efavirenz(69, 70)	91% ↓ Cmin, 71% ↓ AUC of simeprevir. Avoid combination.(20, 62)	6% ↓AUC, 19% ↓ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required.(20, 66)
Etravirine	29% ↓ Cmin, 23% ↓ AUC of etravirine. Use combination with caution, particularly if coadministering with	No clinically significant changes in either drug. No dose adjustment required.(72)	Not recommended with etravirine due to risk of decreased simeprevir concentrations.(20)	Co-administration has not been studied but no expected clinically significant drug interaction

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
	other medications which may further decrease etravirine concentrations (71)			
Rilpivirine	↑ 39% AUC, ↑ 15% Cmax, ↑ 10% Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(73)	↑ 78% AUC, ↑ 49% Cmax, ↑ 93% Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(72)	6% ↑ AUC, 4% ↓ Cmin of simeprevir and 12%↑ AUC 25% ↑ Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(65)	6% ↑ AUC, 5% ↑ Cmax of rilpivirine, not considered clinically significant. No dose adjustment required.(20, 66)
Protease Inhibitors				
Atazanavir/ ritonavir	49% ↓ Ctrough, 35% ↓ AUC of atazanavir. **Avoid combination.**(68, 74)	85% ↑ Cmin of atazanavir. Combination may be used.(70)	**Not recommended** with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20)	No expected clinically significant drug interaction
Darunavir/ ritonavir	59% ↓ Ctrough, 44% ↓ AUC of darunavir and 32% ↓ boceprevir. **Avoid combination.**(68, 74)	40% ↓ AUC and 42% ↓ Cmin of darunavir, 35% ↓ AUC and 32% ↓ Cmin of telaprevir. **Avoid combination.** (70, 75)	2.6-fold ↑ AUC, 1.79-fold ↑ Cmax, 4.58-fold ↑ Cmin of simeprevir and 18% ↑ AUC, 31% ↑ Cmin of darunavir. **Coadministration not recommended.**(20)	37% ↑ AUC, 45% ↑ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required.(20, 66)
Fosamprenavir/ ritonavir	**Not recommended** with ritonavir-boosted protease inhibitors .(68)	47% ↓ AUC and 56% ↓ Cmin of amprenavir. 32% ↓ AUC and 30% ↓ Cmin of telaprevir. **Avoid combination.**(70, 75)	**Not recommended** with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20, 62)	Co-administration has not been studied but no expected clinically significant drug interaction
Lopinavir/ ritonavir	43% ↓ Ctrough, 34% ↓	6% ↑ AUC and 14% ↑	**Not recommended** with	Co-administration has

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
	AUC of lopinavir and 45% ↓ boceprevir. **Avoid combination.**(68, 74, 76)	Cmin of lopinavir, 54 ↓ AUC and 52↓ Cmin of telaprevir. **Avoid combination.**(70, 75, 76)	ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20)	not been studied but no expected clinically significant drug interaction
CCR5 Antagonist				
Maraviroc	Maraviroc AUC ↑ 202%, Cmax ↑ 233% and Ctrough ↑ 178% vs. maraviroc 150 mg BID alone. **Reduce maraviroc dose to 150 mg BID when coadministering with boceprevir**.(77, 78)	Maraviroc AUC ↑ 849%, Cmax ↑ 681% and Ctrough ↑ 917% vs. maraviroc 150 mg BID alone. **Reduce maraviroc dose to 150 mg BID when coadministering with telaprevir.**(77)	No expected clinically significant drug interaction	Co-administration has not been studied but no expected clinically significant drug interaction

Key: = avoid combination = caution/dose adjustment = combination OK

Q8H: every 8 hours; po: orally; Cmin: concentration minimum; AUC: area under the curve; Cmax: concentration maximum; Ctrough: concentration trough; BID: twice a day

Table 3. Summary of Antiretroviral Regimen Recommendations for Patients Who Require Concomitant HIV and Hepatitis C Treatment.

	Recommended	Alternative	NOT Recommended
Sofosbuvir 400 mg daily	No restrictions on antiretroviral choices.	No restrictions on antiretroviral choices.	
Simeprevir 150 mg daily with food	Dolutegravir, raltegravir, or rilpivirine-based regimens.		Ritonavir- or cobicistat-boosted regimens; efavirenz, etravirine, nevirapine
Telaprevir 1125mg BID with food (not low fat)	Atazanavir/ritonavir, dolutegravir, elvitegravir, raltegravir, or rilpivirine-based regimens.	Efavirenz (with increase in telaprevir dose to 1125 mg q8h), etravirine.	Other Protease Inhibitor-based regimens, including: Darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir.
Boceprevir 800 mg q8h with food	Dolutegravir, raltegravir, or rilpivirine-based regimens.		Protease Inhibitor based regimens including: Atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir; Other NNRTI-based regimens including: efavirenz, etravirine, nevirapine

BID: twice daily; Q8h: every 8 hours

NNRTI: non-nucleoside reverse transcriptase inhibitors

Appendix

Table Grading system for recommendations

Classification Description	
Class of Evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial , useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness /efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful
Grade of Evidence	
Level A	Data derives from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies, or standard-of-care.

Adapted from (58, 79, 80)

CANADA

PROVINCE DE QUÉBEC
DISTRICT DE MONTRÉAL

NO: 500-06-000016-960 **COUR SUPÉRIEURE**

Le 19 novembre 1999

SOUS LA PRÉSIDENCE DE
L'HONORABLE NICOLE MORNEAU, J.C.S.

DOMINIQUE HONHON, 3, Place Bretagne, Hull, Québec,

Requérante

c.

PROCUREUR GÉNÉRAL DU CANADA, Complexe Guy-Favreau, Tour est, 200, boul. René-Lévesque ouest, 9e étage, Montréal, Québec
et
PROCUREUR GÉNÉRAL DU QUÉBEC, 1, rue Notre-Dame est, 8e étage, Montréal, Québec
et
SOCIÉTÉ CANADIENNE DE LA CROIX-ROUGE, 2170, boul. René-Lévesque ouest, Montréal, Québec

Intimés

et

FONDS D'AIDE AUX RECOURS COLLECTIFS, 1, rue Notre-Dame est, bureau 10.31, Montréal, Québec
et
LE CURATEUR PUBLIC DU QUÉBEC, 600, boul. René-Lévesque ouest, suite 500, Montréal, Québec

Mis en cause

J.M. 1242

JUGEMENT

LE TRIBUNAL est saisi d'une requête visant à obtenir une ordonnance additionnelle d'approbation d'une transaction présentée par la requérante, Dominique Honhon;

CONSIDÉRANT que le Tribunal a rendu un jugement le 21 septembre 1999 accueillant la requête en approbation d'une transaction présentée par la requérante, Dominique Honhon;

CONSIDÉRANT l'entente intervenue entre les parties modifiant la Convention relative à l'Hépatite C 1986-1990 et ses annexes datée du 15 juin 1999 (ci-après la « Convention de règlement »), contenue à l'Annexe F de la Convention de règlement;

CONSIDÉRANT que les parties ont convenu que les gouvernements PT possèdent l'option de verser des montants périodiques en conformité avec les articles 4.02 et 4.04 de l'Accord de financement de telle sorte que, dans cette éventualité, il ne restera dans le Fonds en Fiducie aucune somme d'argent ou actif des gouvernements PT qui ne serait alloué actuariellement;

CONSIDÉRANT la nature avantageuse des modifications contenues à l'Annexe F de la Convention de règlement;

CONSIDÉRANT que les modifications à la Convention de règlement prévues à l'Annexe F sont également soumises pour approbation dans les provinces de l'Ontario et de la Colombie-Britannique, avec les adaptations nécessaires pour respecter les spécificités de chacune des juridictions;

CONSIDÉRANT que le Tribunal a pris connaissance du projet de jugement à être rendu par l'honorable juge Warren K. Winkler sur une requête similaire présentable en Ontario;

CONSIDÉRANT que les modifications prévues à l'Annexe F tiennent compte de la spécificité du droit applicable dans la province de Québec;

CONSIDÉRANT qu'il est dans l'intérêt des membres et de la justice que le Tribunal entérine les modifications à la Convention de règlement contenues à l'Annexe F de la Convention de règlement, lesquelles sont à l'avantage des membres;

CONSIDÉRANT que la requérante demande d'être dispensée de donner l'avis prévu à l'article 1025 du Code de procédure civile compte tenu de la nature avantageuse des modifications pour les membres et afin d'éviter d'imposer à ceux-ci tout délai additionnel;

PAR CES MOTIFS, LE TRIBUNAL :

ACCUEILLE la requête en approbation additionnelle d'une transaction présentée par la requérante;

PREND ACTE du consentement des parties aux modifications à la Convention de règlement contenues à l'Annexe F;

ENTÉRINE les modifications à la Convention de règlement contenues à l'Annexe F;

DISPENSE la requérante de publier l'avis prévu à l'article 1025 du Code de procédure civile compte tenu de la nature avantageuse desdites modifications pour les membres du recours collectif;

DÉCLARE que le groupe, dont les membres seront liés par le jugement, est défini comme suit :

« i des personnes ayant reçu, au Québec, une transfusion de sang, tel que ci-après défini, entre le 1er janvier 1986 et le 1er juillet 1990 inclusivement et qui sont ou ont été infectées par le virus de l'Hépatite C;

ii d'un époux ou d'un conjoint infecté indirectement par le virus de l'Hépatite C par un époux ou un conjoint qui est une personne décrite au paragraphe (i);

iii d'un enfant infecté indirectement par le virus de l'Hépatite C par un parent qui est une personne décrite aux paragraphes (i) et (ii); ou

iv d'un membre de la famille d'une personne décrite aux paragraphes (i), (ii) ou (iii);

le sang étant défini comme suit :

le sang total et les produits sanguins suivants : les concentrés de globules rouges, les plaquettes, le plasma (frais congelé et stocké) et les globules blancs. Le sang ne comprend pas l'albumine à 5%, l'albumine à 25%, le facteur VIII, le facteur VIII porcin, le facteur IX, le facteur VII, l'immunoglobuline anti-cytomégalovirus, l'immunoglobuline anti-hépatitique B, l'immunoglobuline anti Rh, l'immunoglobuline antivaricelleuse-antizostérienne, l'immunoglobuline sérique, (FEIBA) FEVIII Inhibitor Bypassing Activity, Autoplex (complexe prothrombine), l'immunoglobuline antitétanique, l'immunoglobuline intraveineuse (IVIG) et l'antithrombine III (ATIII); »

DÉCLARE que la Convention de règlement relatif à l'Hépatite C 1986-1990, intervenue en date du 15 juin 1999 ainsi que ses annexes « A », « B », « C », « D », « E » et « F » ci-après décrites :

- Annexe « A » : Régime à l'intention des transfusés infectés par le VHC;
- Annexe « B » : Régime à l'intention des hémophiles infectés par le VHC;
- Annexe « C » : Programme d'aide financière fédéral/ provincial/ territorial pour les personnes indirectement infectées par le VIH;
- Annexe « D » : Accord de financement;

- Annexe « E » : Législation sur les prestations sociales;
- Annexe « F » : Modifications numéro 1 à la Convention de règlement ;

et l'Accord de financement (ci-après appelée « **Convention de règlement** ») sont justes, raisonnables et ont été conclus dans le meilleur intérêt des membres du recours collectif des transfusés infectés par le VHC;

APPROUVE la Convention de règlement et **ORDONNE** aux parties et aux membres liés par la Convention de règlement de s'y conformer;

DÉCLARE qu'à la date d'approbation, le gouvernement fédéral doit payer au fiduciaire, en vertu des paragraphes 4.01 (1) et 4.02 (1) de l'Accord de financement, le montant dû et échu en date du 30 septembre 1999, soit la somme de 846 327 527,00 $, plus les intérêts courus entre cette date et la date de paiement, conformément à l'Accord de financement, plus ou moins de tout ajustement prévu par cet accord.

ORDONNE ET DÉCLARE que le présent jugement n'affectera en aucune façon la Société canadienne de la Croix-Rouge étant donné que les présentes procédures en recours collectif ont été suspendues contre celle-ci par un jugement de

l'honorable juge Blair de la Cour supérieure de l'Ontario daté du 20 juillet 1998, rendu en vertu de la *Loi sur les arrangements avec les créanciers des compagnies* (S.R.C. 1985, ch. C-36) dans une action portant le numéro 98-CL-002970, pareille suspension ayant été prolongée par des ordonnances ultérieures de la même Cour et datées des 19 août 1998, 5 octobre 1998, 18 janvier 1999, 5 mai 1999 et du 28 juillet 1999;

DÉCLARE que les honoraires et déboursés des procureurs de la requérante seront déterminés à une date ultérieure;

DÉCLARE que la Cour procédera ultérieurement à la nomination des personnes appropriées aux postes décrits à la Convention de règlement ;

NOMME Me Pierre R. Lavigne au comité conjoint comme le conseiller aux recours collectifs des transfusés (Québec) et ce, jusqu'à ordre contraire d'un tribunal, selon les termes et conditions et avec les devoirs et responsabilités décrits à ladite Convention de règlement;

DÉCLARE que le mis en cause, le Curateur public du Québec, pourra, par requête pour directives et instructions, s'adresser à cette Cour, selon qu'il le juge approprié;

DISPENSE le mis en cause, le Curateur public du Québec, d'obtenir l'autorisation du tribunal requise pour transiger en faveur de chacune des personnes qu'il représente, pour quelque indemnisation que ce soit en vertu de la Convention de règlement, nonobstant l'article 36 de la *Loi sur le curateur public* (L.R.Q., c. C-81) et **DÉCLARE** que le présent jugement équivaut à l'autorisation requise en vertu de l'article 36 de la *Loi sur le curateur public*;

DÉCLARE que la Convention de règlement constitue une transaction au sens de l'article 2631 du *Code civil du Québec* liant toutes les parties et tous les membres liés par ce règlement;

ORDONNE ET DÉCLARE que soit donné aux membres des recours collectifs et aux membres de leur famille un avis du présent jugement, de la manière à être déterminée par la Cour à une date ultérieure;

DÉCLARE que la date limite pour s'exclure du groupe visé par le règlement sera la date que fixera ultérieurement le Tribunal après avoir approuvé les avis à être publiés;

DÉCLARE que, sous réserve de l'article 1008 du *Code de procédure civile du Québec*, tout membre du groupe ci-avant décrit qui ne s'est pas exclu en présentant au gestionnaire des réclamations une formule d'exclusion dûment remplie dans le délai d'exclusion, sera lié par la présente Convention de règlement et le présent jugement d'approbation;

ORDONNE ET DÉCLARE, conditionnellement à l'approbation de la Convention de règlement par l'honorable juge Smith en Colombie-Britannique et le l'honorable juge Winkler en Ontario, qu'à l'exception de ce qui est prévu ci-avant, le recours collectif institué par madame Dominique Honhon est rejeté sans frais ;

DÉCLARE que la soussignée demeurera saisie du présent dossier à moins de contrordre du Juge en chef;

Nicole Morneau j.c.s.

NICOLE MORNEAU, J.C.S.

COPIE CONFORME
officier autorisé

Me Michel Savonitto
Marchand, Magnan, Melançon, Forget
Me Pierre R. Lavigne
Procureurs de la requérante

Me André Lespérance
Me Nathalie Drouin
Côté & Ouellet
Procureurs du Procureur général du Canada

Me Robert Monette
Me Dany Leduc
Bernard Roy & Ass.
Procureurs du Procureur général du Québec

Me Robert E. Charbonneau
McMaster, Gervais
Procureurs de la Société canadienne de la Croix-Rouge

Me Louise Ducharme
Procureur du Fonds d'aide aux recours collectifs

Me Hélène Laberge
Procureur du Curateur public du Québec.

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Approuvé 15/11/99

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ANNEXE F

MODIFICATION NUMÉRO 1 – 2 NOVEMBRE 1999

La Convention de règlement est modifiée comme suit :

1. Par l'ajout au paragraphe 10.01 de la Convention de règlement des alinéas suivants:

« p.1) Dans le cadre du libre exercice de leur pouvoir discrétionnaire, ordonner, de temps à autre, sur demande de toute partie ou du Comité conjoint, que les fonds et les autres éléments d'actif détenus par le fiduciaire en vertu de la Convention de règlement et qui ne font pas l'objet d'une attribution actuarielle soient en tout ou en partie :

(i) attribués aux membres des recours collectifs et/ou aux membres de la famille;

(ii) attribués de toute manière dont on peut raisonnablement s'attendre qu'elle bénéficie aux membres des recours collectifs et/ou aux membres de la famille, même si l'attribution ne prévoit pas le versement d'une indemnité aux membres des recours collectifs et/ou aux membres de la famille;

(iii) payés, en tout ou en partie, aux gouvernements FPT, à certains ou à un seul d'entre eux, compte tenu de la source

des fonds et des autres éléments d'actif que comprend le fonds en fiducie; et/ou

(iv) conservés, en tout ou en partie, dans le fonds en fiducie;

de la manière que, dans le cadre du libre exercice de leur pouvoir discrétionnaire, les tribunaux estimeront raisonnable en tenant compte de toutes les circonstances, pourvu que, dans la distribution, aucune discrimination n'ait lieu selon l'endroit où le membre du recours collectif a reçu du sang ou selon l'endroit où il réside;

« p.2) Dans le cadre du libre exercice de leur pouvoir discrétionnaire qui leur est conféré par l'alinéa p.1) ci-devant, les tribunaux peuvent prendre en considération, mais sans être liés par aucun d'entre eux, notamment les facteurs suivants :

(i) le nombre de membres des recours collectifs et de membres de la famille;

(ii) l'expérience du fonds en fiducie;

(iii) le fait que les indemnités prévues par les régimes peuvent, dans certains cas, ne pas refléter le régime de responsabilité en matière extra-contractuelle;

(iv) l'article 1036 du *Code de procédure civile du Québec*;

(v) la question de savoir si l'intégrité de la Convention de règlement sera maintenue et si les versements des indemnités prévues dans les régimes seront assurés;

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(vi) la question de savoir si la progression de la maladie est très différente de celle prévue dans le modèle médical utilisé dans le rapport actuariel Eckler;

(vii) le fait que les membres des recours collectifs et les membres de la famille assument le risque d'insuffisance du fonds en fiducie;

(viii) le fait que les contributions des gouvernements FPT sont limitées en vertu de la Convention de règlement;

(ix) la source des fonds et des autres éléments d'actif que comprend le fonds en fiducie;

(x) tout autre fait que les tribunaux estiment important. »

2. Les paragraphes 11.02 de la Convention de règlement et 6.03 de l'Accord de financement sont abrogés et remplacés par ce qui suit:

« 11.02 (1) Le montant à payer ou payable par les gouvernements FPT en vertu de la Convention de règlement et de l'Accord de financement doit être réduit de 10,533,000$, en date du 30 septembre 1999; soit la somme de 10,000,000 $ représentant la valeur actualisée estimée du coût excédentaire pour le fonds en fiducie du règlement des actions intentées ou poursuivies par ceux qui s'excluent ou qui sont réputés s'exclure d'un recours collectif et par ceux qui intentent une action récursoire ou en garantie ou qui présentent une réclamation, une demande ou toute autre procédure contre un gouvernement FPT dont l'objet ou la cause est, de quelque manière

que ce soit : (i) dans le cas d'un membre d'un recours collectif des transfusés ou d'un membre de la famille aux termes du Régime à l'intention des transfusés infectés par le VHC, l'infection d'une personne directement infectée par le VHC pendant la période visée par les recours collectifs; ou (ii) dans le cas d'un membre d'un recours collectif des transfusés ou des hémophiles ou d'un membre de la famille des transfusés ou des hémophiles aux termes du Régime à l'intention des hémophiles infectés par le VHC, l'infection d'un hémophile ou d'un transfusé directement infecté par le VHC provenant du sang (y compris, dans chaque cas, l'infection d'une personne indirectement infectée) (collectivement appelés les personnes qui s'excluent); et la somme de 533,000$ représentant la valeur actualisée du tiers des coûts liés à la défense contre les actions poursuivies par les personnes qui s'excluent. Pour plus de certitude, toute personne qui est membre d'un recours collectif ci-avant défini peut participer aux régimes créés par la Convention de règlement.

« 11.02 (2) Sur remise au fiduciaire d'une copie d'un jugement final (tel que défini au paragraphe 1.07 de la Convention de règlement) obtenu par une personne qui s'exclut contre les gouvernements FPT, certains ou un seul d'entre eux, ou d'une transaction conclue par une personne qui s'exclut et les gouvernements FPT, certains ou un seul d'entre eux, et d'une copie de l'ordonnance finale d'un

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tribunal homologuant une transaction, les gouvernements FPT ou leurs mandataires doivent recevoir à partir du fond en fiducie :

(i) suivant la date de ce jugement ou de ce règlement, un montant égal au montant que la personne qui s'exclut aurait eu droit de recevoir du fonds en fiducie s'il avait été admissible à un régime; et

(ii) un versement forfaitaire, sur approbation de l'un des tribunaux, en vue de couvrir le montant que la personne qui s'exclut aurait pu être en droit de recevoir de temps à autre du fonds en fiducie s'il avait été admissible à un régime, ce montant devant être calculé conformément à un protocole devant être approuvé par les tribunaux;

pourvu, cependant, que dans aucun cas, le montant devant être versé à partir du fonds en fiducie aux gouvernements FPT, à certains ou à un seul d'entre eux n'excède le montant du jugement ou du règlement versé à la personne qui s'exclut par les gouvernements FPT, certains ou un seul d'entre eux, plus les intérêts courus sur ce montant.

« 11.02 (3) Aucun autre montant ne doit être payé à partir du fonds en fiducie pour régler une action poursuivie par une personne qui s'exclut, pour satisfaire à un jugement obtenu sur une action intentée par une personne qui s'exclut ou pour indemniser les gouvernements FPT, certains ou un seul d'entre eux de tout jugement ou de tout

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règlement intervenu par suite de toute action intentée ou poursuivie par une personne qui s'exclut.»

Le Régime à l'intention des transfusés (Annexe A) est modifié comme suit :

3. Le sous-paragraphe a) de la définition de « Personne directement infectée » au paragraphe 1.01 est modifié comme suit :

   - remplacer le «;» par un «.» à la fin du sous-paragraphe a);

     et

   - ajouter la phrase suivante à la fin dudit sous-paragraphe a) :

     « Une personne atteinte ou ayant été atteinte de thalassémie majeure n'est pas visée par le présent sous-paragraphe a); »

4. Par l'ajout d'un paragraphe 4.10 :

   « Les personnes directement infectées atteintes de thalassémie majeure ont le droit de présenter les preuves requises à des fins d'indemnisation et de recevoir les indemnités prévues par le Régime à l'intention des hémophiles infectés par le VHC, ***mutatis mutandis***, comme si elles étaient des hémophiles directement infectés, et elles sont réputées être, pour les fins de la Convention et du Régime à l'intention des hémophiles infectés par le VHC, des hémophiles directement infectés, sous réserve que la condition figurant au paragraphe 4.01(5) du Régime à l'intention des hémophiles infectés par le VHC ne

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s'applique pas, et leur conjoint et leurs enfants qui sont des personnes indirectement infectées au sens du régime à l'intention des transfusés ainsi que les membres de la famille ont également le droit de présenter les preuves requises à des fins d'indemnisation et de recevoir les indemnités prévues par le Régime à l'intention des hémophiles infectés par le VHC, sous réserve que la condition figurant au paragraphe 4.01(5) du Régime à l'intention des hémophiles infectés par le VHC ne s'applique pas. »

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