

**Protocol:**  
**Systematic Review and Meta-analysis of Hepatitis C**  
**Treatments for Non-Pregnant, Treatment-Naïve Adults**

Date: Nov. 25, 2015

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## Table of Contents

|  |           |
|--|-----------|
| <b>Section I. Purpose and Background.....</b>                                      | <b>4</b>  |
| <b>Section II. Research Questions.....</b>   | <b>4</b>  |
| <b>Eligibility Criteria.....</b>   | <b>5</b>  |
| Table 1 - Inclusion and Exclusion Criteria- Treatment questions (KQ1 and KQ2)..... | 5         |
| <b>Section III: Methods .....</b>  | <b>6</b>  |
| Literature Search Strategy .....   | 6         |
| Study Selection.....   | 6         |
| Data Extraction and Quality Assessments .....                                      | 7         |
| Analysis Plan.....   | 7         |
| Data Analysis.....   | 7         |
| <b>Section IV: Planned Schedule and Timeline .....</b>                             | <b>8</b>  |
| <b>References.....</b>   | <b>9</b>  |
| <b>Appendix A: Search Strategy (up until February 2015).....</b>                   | <b>11</b> |
| <b>Appendix B: Search Strategy (February 2015 to November 2015) .....</b>          | <b>14</b> |

## Section I. Purpose and Background

The Hepatitis C virus (HCV) is a virus that attacks the liver and can cause liver disease.<sup>1</sup> It is estimated that 3% of the world's population has a chronic hepatitis C virus infection.<sup>2</sup> In 2011, it was estimated that 0.64% of Canadians, or approximately 220,000 persons, had chronic HCV infection, but that 44% of cases were not diagnosed.<sup>3</sup> Individuals living with undiagnosed HCV infection remain infectious and can potentially transmit the virus to others through blood-to-blood contact.<sup>1</sup>

An initial screening test is conducted to detect HCV antibodies in the blood. If the screening test is positive, an additional blood test is conducted to detect HCV RNA in the blood to confirm current infection with HCV.<sup>1</sup> Currently, there are no national or provincial screening programs in Canada for HCV infection.<sup>4</sup> In 2009, the College of Family Physicians of Canada and the Public Health Agency of Canada recommended that anyone with risk behaviours or potential exposures to HCV and those with clinical clues that raise suspicion of possible HCV infection receive testing.<sup>5</sup> However, evidence suggested that risk-factor based testing have failed to identify a large proportion of infected people, possibly due to inaccurate reporting of risk-status by patients or lack of time and expertise necessary to conduct a proper risk assessment by health providers.<sup>6</sup> So in 2012, the Canadian Liver Foundation issued a statement recommending that all adults born between 1945 and 1975 be tested once for HCV infection.<sup>7</sup>

Treatment of HCV infection is through antiviral therapy and effectiveness is often evaluated by sustained virological response (SVR), or undetectable serum levels of HCV RNA, after a defined period post-treatment.<sup>8</sup> Until 2011, the standard of care for treatment of chronic HCV infection was pegylated interferon alpha + ribavirin (PR) administered for 48 weeks<sup>9</sup>, resulting in SVR rates between 40%-80% depending on the HCV genotype of the patient.<sup>10</sup> Since then, the standard of care has changed due to regulatory approvals for use of direct-acting antivirals (DAAs) such as boceprevir, telaprevir, simeprevir and sofosbuvir, which, in combination with PR, offer substantial improvement in SVR rates compared to PR alone.<sup>10,11</sup> Besides improvements in SVR rates, some newer treatments are interferon-free, resulting in fewer side effects, or are all-oral treatments that reduce the burden on patients compared to injection-based treatments.<sup>12</sup>

The purpose is to conduct a systematic review of published research evidence on the effectiveness and harms of Hepatitis C treatment in treatment-naïve non-pregnant adults that will provide part of the evidence required for the Canadian Task Force on Preventive Health Care to develop recommendations on screening for hepatitis C infection.

## Section II. Research Questions

The key questions for this review are as follows:

KQ1) What is the comparative clinical benefit of treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naïve?

KQ2) What are the frequency of harms associated with treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naïve?

## Eligibility Criteria

The inclusion and exclusion criteria that will be used to select studies to answer the key questions of this review are summarized in Table 1.

**Table 1 - Inclusion and Exclusion Criteria- Treatment questions (KQ1 and KQ2)**

|                      | Inclusion   | Exclusion   |
|----------------------|---|---|
| <b>Population</b>    | Treatment-naïve non-pregnant adults<br><br><i>* For studies wherein data on only treatment-naïve patients cannot be extracted, study populations comprised of at least 80% treatment-naïve individuals will also be included.</i>   | Post-transplant patients; people with HIV; hemodialysis patients; people with occupational exposure |
| <b>Interventions</b> | Treatment (any that is currently available for use in Canada and any emerging regimens that are anticipated to become available in Canada by February 2016) of HCV for all genotypes (1-6)  |   |
| <b>Comparators</b>   | KQ1: PR48 (Pegylated interferon plus ribavirin for 48 weeks)<br><br><i>* For single arm trials, pre-established baseline/historical SVR rates will be used as comparator.</i>   |   |
| <b>Outcomes</b>      | KQ1:<br><br><i>Long-term outcomes:</i> Mortality (hepatic & all cause), Cirrhosis, Hepatocellular carcinoma, Hepatic decompensation, Need for liver transplantation, Quality of life (all scales reported)<br><br><i>Intermediate outcomes:</i> Reduced HCV transmission, Sustained virological response, Improvement in liver histology.<br><br>KQ2:<br><br>Withdrawal due to adverse events, Psychological adverse events, Neutropenia, Flu-like symptoms, Anemia, rash |   |
| <b>Settings</b>      | Settings where treatment for HCV is commonly or may be performed (e.g., specialized centers)  |   |
| <b>Study designs</b> | Randomized or non-randomized, controlled or uncontrolled, interventional studies.   |   |
| <b>Language</b>      | English   |   |
| <b>Search</b>        | No limits   |   |

|           |  |  |
|-----------|--|--|
| timeframe |  |  |
|-----------|--|--|

## Section III: Methods

To evaluate the evidence on treatment for HCV infection, the following will be completed: (1) conduct a literature search using a systematic search strategy OR conduct an update of a previous systematic search strategy; (2) review and select studies for analysis using pre-defined inclusion and exclusion criteria; (3) extract data from included studies; (4) assess the methodological quality of each study using validated tools; and (5) synthesize and evaluate the strength and quality of the evidence on each outcome of interest.

Two reviewers will extract and verify data. The quality of evidence for each outcome will be assessed separately by two evaluators using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolkit. Additional information is reported in the Data Extraction and Quality Assessments section.

The systematic review to address key questions related to treatment (KQ6 to 7) will be conducted by the Prevention Guidelines Division at PHAC. The systematic review will follow the methodology as recommended in the GRADE<sup>13</sup> and Cochrane<sup>14</sup> methods for systematic reviews.

### *Literature Search Strategy*

The full search strategies are reported in Appendix A and B.

In 2015, CADTH conducted a systematic review on the efficacy and safety of Hepatitis C regimens that were either currently approved for use in Canada, or were considered to have a high likelihood of regulatory approval in Canada by February 2016, and were of clinical relevance due to their inclusion in either a Canadian or US guideline.<sup>11</sup> Since these are the same Hepatitis C regimens of interest for the CTFPHC treatment review, it was decided that the CADTH literature search strategy will be used for this review (Appendix A). For retrieval of articles published up until February 4, 2015, the list of articles that were eligible for full-text article screening (n=238) in the CADTH Therapeutic Review will be assessed further for possible inclusion. For retrieval of articles published since then, a recreation of the search strategy used for the CADTH Therapeutic Review on Drugs for Chronic Hepatitis C Infection: Clinical Review July 2015<sup>11</sup> will be conducted by a Health Canada librarian, while an update of the search strategy for grey literature would be conducted by a scientific officer from the PGD project team (Appendix B).

### *Study Selection*

Two reviewers will independently screen abstracts relevant to the research questions. Full texts of potentially relevant articles will be retrieved and independently assessed by two reviewers for possible inclusion based on the pre-determined selection criteria outlined in TABLE 1. Consensus will be required for inclusion. Conflicts at this level will be resolved by discussion between the two reviewers. A third team member will be consulted to resolve any continued disagreements. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.<sup>15</sup>

### *Data Extraction and Quality Assessments*

For each included study, two independent reviewers will extract data about the population, intervention, comparator(s), study design, results, and primary conclusions. Each reviewer will verify the accuracy and completeness of the other's data extraction. Disagreements will be resolved through discussion and/or third party consultation if consensus cannot be reached. We will contact study authors for missing or incomplete data, as necessary.

Two reviewers will independently assess the quality of each included study using the assessment tool that is most appropriate. Quality assessment will involve a two-step process: first we will critically appraise the methodological quality of all comparative studies; next we will assess the strength and quality of the evidence on each outcome of interest. We will use the AMSTAR tool<sup>16</sup> to critically appraise all systematic reviews and meta-analyses; the Cochrane Risk of Bias tool<sup>14</sup> for RCTs, the Newcastle-Ottawa Scale<sup>17</sup> for Non-Randomized Studies of Interventions<sup>18</sup> as appropriate. A modified version of the Drummond Checklist will be used to assess disease-progression modelling studies.<sup>19</sup> The critical appraisal of qualitative studies will follow criteria outlined in the CASP checklist: [http://media.wix.com/ugd/dded87\\_29c5b002d99342f788c6ac670e49f274.pdf](http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf)

We will use the GRADE system<sup>13</sup> to assess the strength and quality of the evidence for all outcomes ranked by the CTFPHC working group members and the patient sample as critical or important.

### *Analysis Plan*

Each study design will be analyzed separately (i.e., data from randomized and non-randomized control studies will not be quantitatively pooled with data from observational studies). Separate analyses will be conducted on data from observational studies with controls (for both benefits and harms) and without controls (for harms only). Data on sustained virological response (SVR) from single arm trials will be compared to historical rates and rates obtained from the comparator group (PR48) of the controlled studies analyses conducted in this review.

The methodological, clinical and statistical heterogeneity will be assessed within the GRADE domains (i.e., directness across studies, risk of bias, and consistency). We will do a sensitivity analysis based on risk of bias rating (high, unclear, low) for primary outcomes of interest and number needed to treat and number needed to harm will be calculated based on Cochrane's recommended method.<sup>14</sup> To assess for publication bias, funnel plots will be created pending sufficient number of studies for inclusion (minimum 10 studies).

### *Data Analysis*

The Cochrane Review Manager software version 5.3 will be used for meta-analyses of the pooled data for the outcomes of interest. Randomized and non-randomized study designs will be analyzed separately. Analyses of dichotomous outcomes such as frequency of harms will be summarized using relative risks (RRs) and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using differences in means and 95% CIs. When different scales are used, analyses of continuous outcomes will be summarized as standardised mean differences (SMD) with 95% CIs.

For outcomes of benefits of treatment for HCV, further sub-group and sensitivity analyses will be conducted where possible to evaluate statistical stability and effect on statistical heterogeneity. The Cochran's Q ( $\alpha=0.05$ ) will be employed to detect statistical heterogeneity and the  $I^2$  statistic will be used to quantify the magnitude of statistical heterogeneity between studies.<sup>14</sup>

## **Section IV: Planned Schedule and Timeline**

- Draft protocol: November 2015
- Final Protocol: November 2015
- Draft Evidence Review: January 2016
- Final Evidence Review: March 2016



## References

1. Canadian Liver Foundation. Hepatitis C. [http://www.liver.ca/liver-disease/types/viral\\_hepatitis/Hepatitis\\_C.aspx](http://www.liver.ca/liver-disease/types/viral_hepatitis/Hepatitis_C.aspx). Accessed 11/04, 2015.
2. Mohd Hanafiah K, Groeger J, Flaxman A, Wiersma S. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013;57(4):1333.
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4. Shah HA, Heathcote J, Feld JJ. A canadian screening program for hepatitis C: Is now the time? *CMAJ*. 2013;185(15):1325-1328. doi: 10.1503/cmaj.121872 [doi].
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7. Canadian Liver Foundation. Position statement - hepatitis C testing. [http://www.liver.ca/files/PDF/Position\\_Statements/CLF\\_Position\\_Statements\\_-\\_Testing\\_for\\_hepatitis\\_C\\_-\\_FINAL.pdf](http://www.liver.ca/files/PDF/Position_Statements/CLF_Position_Statements_-_Testing_for_hepatitis_C_-_FINAL.pdf). Updated 2012. Accessed 11/04, 2015.
8. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. 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. doi: 16644 [pii].
9. Pawlotsky JM. Hepatitis C virus: Standard-of-care treatment. *Adv Pharmacol*. 2013;67:169-215. doi: 10.1016/B978-0-12-405880-4.00005-6 [doi].
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11. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH therapeutic review: Drugs for chronic hepatitis C infection: Clinical review. [DRAFT] july 2015. .
12. Dugum M, O'Shea R. Hepatitis C virus: Here comes all-oral treatment. *Cleve Clin J Med*. 2014;81(3):159-172. doi: 10.3949/ccjm.81a.13155 [doi].
13. Schünemann H, Brożek J, Guyatt G, Oxman A, ed. *GRADE handbook for grading quality of evidence and strength of recommendations*. updated october 2013. the GRADE working group, 2013. available from [www.guidelinedevelopment.org/handbook](http://www.guidelinedevelopment.org/handbook). .

14. Higgins JPT, Green S, ed. *Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated march 2011]. the cochrane collaboration, 2011. available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org)* .
15. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ*. 2015;349:g7647. doi: 10.1136/bmj.g7647 [doi].
16. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*. 2007;15(7):10.
17. Wells GA, Shea B, O'Connell D, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Updated 2011. Accessed 05/25, 2011.
18. A cochrane risk of bias assessment tool: For non-randomized studies of interventions (ACROBAT-NRSI). <http://bmg.cochrane.org/cochrane-risk-bias-assessment-tool-non-randomized-studies-interventions-acrobat-nrsi>. Accessed 11, 2015.
19. Canadian Task Force on Preventive Health Care. Appendix X: Process to incorporate and assess the quality of modelling studies that address key questions. in: Procedure manual. <http://canadiantaskforce.ca/methods/procedural-manual/>. Accessed 11, 2015.

## Appendix A: Search Strategy (up until February 2015)

### Treatment

(Source: CADTH Therapeutic Review on Drugs for Chronic Hepatitis C Infection: Clinical Review July 2015<sup>11</sup>)

### OVERVIEW

Interface: Ovid  
Databases: Embase 1974 to present  
MEDLINE Daily and MEDLINE 1946 to present  
MEDLINE In-Process & Other Non-Indexed Citations  
EBM Reviews - Cochrane Central Register of Controlled Trials  
December 2014  
**Note:** Subject headings have been customized for each database.  
Duplicates between databases were removed in Ovid.  
Date of Search: February 4, 2015  
Alerts: Bi-weekly search updates until project completion  
Study Types: No study design filters used  
Limits: Date limit: None  
Language limit: English  
Conference abstracts: excluded  
Animal filter used

### SYNTAX GUIDE

/ At the end of a phrase, searches the phrase as a subject heading  
.sh At the end of a phrase, searches the phrase as a subject heading  
exp Explode a subject heading  
\* Before a word, indicates that the marked subject heading is a primary topic;  
or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings  
adj Requires words are adjacent to each other (in any order)  
.ti Title  
.ab Abstract  
.hw Heading Word; usually includes subject headings and controlled vocabulary  
.nm Name of Substance Word  
.ot Original title  
.pt Publication type  
.rn CAS registry number  
pmez Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present  
oemezd Ovid database code; Embase 1974 to present, updated daily  
cctr Ovid database code; Cochrane Central Register of Controlled Trials

### # Searches

- 1 (incivek or incivo or telaprevir\* or telapravir\* or teleprvir\* or teleprevir\* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab.
- 2 \*telaprevir/
- 3 (boceprevir\* or bocepravir\* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab.
- 4 \*boceprevir/
- 5 (sofosbuvir\* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI

- 7976 or PSI7976 or Sovaldi or Virunon).ti,ab.
- 6 \*sofosbuvir/
- 7 (simeprevir\* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab.
- 8 \*simeprevir/
- 9 (ledipasvir\* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab.
- 10 \*ledipasvir/
- 11 (paritaprevir\* or veruprevir\* or ABT 450\* or ABT450\*).ti,ab.
- 12 \*paritaprevir/ or \*veruprevir/
- 13 (ombitasvir\* or ABT 267 or ABT267).ti,ab.
- 14 \*ombitasvir/
- 15 (dasabuvir\* or ABT 333 or ABT333).ti,ab.
- 16 \*dasabuvir/
- 17 (daclatasvir\* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab.
- 18 \*daclatasvir/
- 19 (asunaprevir\* or Sunvepra or BMS 650032 or BMS650032).ti,ab.
- 20 \*asunaprevir/
- 21 (grazoprevir\* or MK 5172 or MK5172).ti,ab.
- 22 \*grazoprevir/
- 23 (elbasvir\* or MK 8742 or MK8742).ti,ab.
- 24 \*elbasvir/
- 25 (beclabuvir\* or BMS 791325 or BMS791325).ti,ab.
- 26 \*beclabuvir/
- 27 (GS5816 or GS 5816).ti,ab.
- 28 (ABT-530 or ABT530).ti,ab.
- 29 (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab.
- 30 or/1-29
- 31 30 use oemezd
- 32 31 not conference abstract.pt.
- 33 (incivek or incivo or telaprevir\* or telapravir\* or telepravir\* or teleprevir\* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab,ot,sh,hw,rn,nm.
- 34 (402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm.
- 35 (boceprevir\* or bocepravir\* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab,ot,sh,hw,rn,nm.
- 36 (394730-60-0 or 89BT58KELH).rn,nm.
- 37 (sofosbuvir\* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab,ot,sh,hw,rn,nm.
- 38 (1190307-88-0 or WJ6CA3ZU8B).rn,nm.
- 39 (simeprevir\* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab,ot,sh,hw,rn,nm.
- 40 (923604-59-5 or 9WS5RD66HZ).rn,nm.
- 41 (ledipasvir\* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab,ot,sh,hw,rn,nm.
- 42 (1256388-51-8 or 013TE6E4WV).rn,nm.
- 43 (paritaprevir\* or veruprevir\* or ABT 450\* or ABT450\*).ti,ab,ot,sh,hw,rn,nm.
- 44 (1216941-48-8 or OU2YM37K86).rn,nm.
- 45 (ombitasvir\* or ABT 267 or ABT267).ti,ab,ot,sh,hw,rn,nm.
- 46 (1258226-87-7 or 2302768XJ8).rn,nm.
- 47 (dasabuvir\* or ABT 333 or ABT333).ti,ab,ot,sh,hw,rn,nm.
- 48 (1132935-63-7 or DE54EQW8T1).rn,nm.
- 49 (daclatasvir\* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab,ot,sh,hw,rn,nm.
- 50 (1009119-64-5 or LI2427F9CI).rn,nm.
- 51 (asunaprevir\* or Sunvepra or BMS 650032 or BMS650032).ti,ab,ot,sh,hw,rn,nm.
- 52 (630420-16-5 or S9X0KRJ00S).rn,nm.
- 53 (grazoprevir\* or MK 5172 or MK5172).ti,ab,ot,sh,hw,rn,nm.

**54** (1350462-55-3 or 1350514-68-9 or 4O2AB118LA or 8YE81R1X1J).rn,nm.  
**55** (elbasvir\* or MK 8742 or MK8742).ti,ab,ot,sh,hw,rn,nm.  
**56** (1370468-36-2 or 632L571YDK).rn,nm.  
**57** (beclabuvir\* or BMS 791325 or BMS791325).ti,ab,ot,sh,hw,rn,nm.  
**58** (958002-33-0 or MYW1X5CO9S).rn,nm.  
**59** (GS5816 or GS 5816).ti,ab,ot,sh,hw,rn,nm.  
**60** (ABT-530 or ABT530).ti,ab,ot,sh,hw,rn,nm.  
**61** (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab,ot,sh,hw,rn,nm.  
**62** or/33-61  
**63** 62 use pmez,cctr  
**64** 32 or 63  
**65** exp animals/  
**66** exp animal experimentation/ or exp animal experiment/  
**67** exp models animal/  
**68** nonhuman/  
**69** exp vertebrate/ or exp vertebrates/  
**70** or/65-69  
**71** exp humans/  
**72** exp human experimentation/ or exp human experiment/  
**73** or/71-72  
**74** 70 not 73  
**75** 64 not 74  
**76** 75 use cctr  
**77** 76 not Journal: conference abstract.pt.  
**78** 75 use pmez,oomezd  
**79** limit 78 to english language  
**80** 77 or 79  
**81** remove duplicates from 80

## OTHER DATABASES

|  |  |
|--|--|
| PubMed                                   | Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.                 |
| Trial registries<br>(Clinicaltrials.gov) | Same keywords, limits used as per MEDLINE search. Search limited to completed trials with study results. |

## Grey Literature

|                 |  |
|-----------------|--|
| Date of Search: | February 2015  |
| Keywords:       | Hepatitis C, telaprevir, boceprevir, simeprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816 and ABT-530 |
| Limits:         | No date limit, English only  |

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)

## Appendix B: Search Strategy (February 2015 to November 2015)

### Drugs for Chronic Hepatitis C Infection

Search conducted by the Health Canada Library (Update – February 4, 2015 to November 18, 2015)

Database(s): **Embase** 1974 to 2015 November 18

Search Strategy:

| #  | Searches   | Results |
|----|--|---------|
| 1  | (incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab. | 2644    |
| 2  | *telaprevir/   | 1333    |
| 3  | (boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab.   | 1817    |
| 4  | *boceprevir/   | 842     |
| 5  | (sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab.   | 1227    |
| 6  | *sofosbuvir/   | 674     |
| 7  | (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab.   | 686     |
| 8  | *simeprevir/   | 301     |
| 9  | (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab.   | 321     |
| 10 | *ledipasvir/   | 65      |
| 11 | (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab.   | 226     |
| 12 | *paritaprevir/ or *veruprevir/   | 27      |
| 13 | (ombitasvir* or ABT 267 or ABT267).ti,ab.  | 210     |
| 14 | *ombitasvir/   | 42      |
| 15 | (dasabuvir* or ABT 333 or ABT333).ti,ab.   | 201     |
| 16 | *dasabuvir/  | 86      |
| 17 | (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab.  | 536     |
| 18 | *daclatasvir/  | 272     |
| 19 | (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab.   | 217     |

|    |   |         |
|----|---|---------|
| 20 | *asunaprevir/   | 129     |
| 21 | (grazoprevir* or MK 5172 or MK5172).ti,ab.                    | 117     |
| 22 | *grazoprevir/   | 15      |
| 23 | (elbasvir* or MK 8742 or MK8742).ti,ab.                       | 63      |
| 24 | *elbasvir/  | 13      |
| 25 | (beclabuvir* or BMS 791325 or BMS791325).ti,ab.               | 55      |
| 26 | *beclabuvir/  | 19      |
| 27 | (GS5816 or GS 5816).ti,ab.                                    | 19      |
| 28 | (ABT-530 or ABT530).ti,ab.                                    | 7       |
| 29 | (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab. | 24      |
| 30 | or/1-29   | 5154    |
| 31 | 30 not conference abstract.pt.                                | 2463    |
| 32 | limit 31 to (human and english language)                      | 1988    |
| 33 | remove duplicates from 32                                     | 1849    |
| 34 | 2015\$.dd,em.   | 1906041 |
| 35 | 33 and 34   | 703     |

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present

Search Strategy:

| # | Searches  | Results |
|---|---|---------|
| 1 | (incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab,ot,sh,hw,rn,nm. | 1306    |
| 2 | (402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm.   | 740     |
| 3 | (boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab,ot,sh,hw,rn,nm.   | 798     |
| 4 | (394730-60-0 or 89BT58KELH).rn,nm.  | 503     |
| 5 | (sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab,ot,sh,hw,rn,nm.   | 646     |
| 6 | (1190307-88-0 or WJ6CA3ZU8B).rn,nm.   | 254     |

|    |   |      |
|----|---|------|
| 7  | (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab,ot,sh,hw,rn,nm. | 334  |
| 8  | (923604-59-5 or 9WS5RD66HZ).rn,nm.  | 146  |
| 9  | (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab,ot,sh,hw,rn,nm.                                     | 155  |
| 10 | (1256388-51-8 or 013TE6E4WV).rn,nm.   | 52   |
| 11 | (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab,ot,sh,hw,rn,nm.   | 95   |
| 12 | (1216941-48-8 or OU2YM37K86).rn,nm.   | 0    |
| 13 | (ombitasvir* or ABT 267 or ABT267).ti,ab,ot,sh,hw,rn,nm.  | 91   |
| 14 | (1258226-87-7 or 2302768XJ8).rn,nm.   | 0    |
| 15 | (dasabuvir* or ABT 333 or ABT333).ti,ab,ot,sh,hw,rn,nm.   | 81   |
| 16 | (1132935-63-7 or DE54EQW8T1).rn,nm.   | 0    |
| 17 | (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab,ot,sh,hw,rn,nm.                    | 283  |
| 18 | (1009119-64-5 or LI2427F9CI).rn,nm.   | 0    |
| 19 | (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab,ot,sh,hw,rn,nm.   | 109  |
| 20 | (630420-16-5 or S9X0KRJ00S).rn,nm.  | 0    |
| 21 | (grazoprevir* or MK 5172 or MK5172).ti,ab,ot,sh,hw,rn,nm.   | 40   |
| 22 | (1350462-55-3 or 1350514-68-9 or 4O2AB118LA or 8YE81R1X1J).rn,nm.   | 0    |
| 23 | (elbasvir* or MK 8742 or MK8742).ti,ab,ot,sh,hw,rn,nm.  | 25   |
| 24 | (1370468-36-2 or 632L571YDK).rn,nm.   | 0    |
| 25 | (beclabuvir* or BMS 791325 or BMS791325).ti,ab,ot,sh,hw,rn,nm.  | 24   |
| 26 | (958002-33-0 or MYW1X5CO9S).rn,nm.  | 0    |
| 27 | (GS5816 or GS 5816).ti,ab,ot,sh,hw,rn,nm.   | 3    |
| 28 | (ABT-530 or ABT530).ti,ab,ot,sh,hw,rn,nm.   | 0    |
| 29 | (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab,ot,sh,hw,rn,nm.  | 20   |
| 30 | or/1-29   | 2395 |
| 31 | 30 not (conference abstract or Journal: conference abstract).pt.  | 2395 |



|    |   |         |
|----|---|---------|
| 32 | limit 31 to (english language and humans) | 1630    |
| 33 | remove duplicates from 32                 | 1433    |
| 34 | 2015\$.dc,ed.                             | 1516769 |
| 35 | 33 and 34                                 | 428     |

Database(s): **COCHRANE LIBRARY**

Search Strategy as searched in <http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>:

| #  | Searches   | Results |
|----|--|---------|
| 1  | (incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950) all text | 236     |
| 2  | (boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520) all text   | 182     |
| 3  | (sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon) all text   | 146     |
| 4  | (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad) all text   | 80      |
| 5  | (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796) (Word variations have been searched) all text  | 55      |
| 6  | (paritaprevir* or veruprevir* or ABT 450* or ABT450*) (Word variations have been searched) all text  | 66      |
| 7  | (ombitasvir* or ABT 267 or ABT267) (Word variations have been searched) all text   | 54      |
| 8  | (dasabuvir* or ABT 333 or ABT333) (Word variations have been searched) all text  | 52      |
| 9  | (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza) all text  | 73      |
| 10 | (asunaprevir* or Sunvepra or BMS 650032 or BMS650032) all text   | 45      |
| 11 | (grazoprevir* or MK 5172 or MK5172) (Word variations have been searched) all text  | 20      |
| 12 | (elbasvir* or MK 8742 or MK8742) (Word variations have been searched) all text   | 12      |

|    |   |      |
|----|---|------|
| 13 | (beclabuvir* or BMS 791325 or BMS791325) all text   | 17   |
| 14 | (GS5816 or GS 5816) all text  | 7    |
| 15 | (Viekira or Viekirax or Exviera or Holkira or Harvoni) all text                                     | 2    |
| 16 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 | 704  |
| 17 | [Animals] explode all   | 7358 |
| 18 | [Animal Experimentation] explode all  | 4    |
| 19 | [Models, Animal] explode all  | 355  |
| 20 | [Vertebrates] explode all   | 5939 |
| 21 | #17 or #18 or #19 or #20  | 7412 |
| 22 | #16 not #21   | 703  |
| 23 | #16 not #21 Limit=Online Publication Date from Feb2015 to Nov 2015                                  | 11   |

Database(s): **ClinicalTrials.gov**

Search Strategy as searched in clinicaltrials.gov:

| # | Searches   | Results |
|---|--|---------|
| 1 | incivek OR incivo OR telaprevir* OR telaprevir* OR teleprevir* OR teleprevir* OR VX-950 OR VX950 OR LY-570310 OR LY570310 OR MP-424 OR MP424 OR VRT-111950 OR VRT111950   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015 | 5       |
| 2 | boceprevir* OR boceprevir* OR victrelis OR "sch 503034" OR sch503034 OR "ebp 520" OR ebp520   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015   | 14      |
| 3 | sofosbuvir* OR "GS 7977" OR GS7977 OR "PSI 7977" OR PSI7977 OR "PSI 7851" OR PSI7851 OR "PSI 7976" OR PSI7976 OR Sovaldi OR Virunon   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015                                     | 15      |
| 4 | simeprevir* OR TMC435 OR "TMC 435" OR TMC435350 OR "TMC 435350" OR Galexos OR Olysio OR Sovriad   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015   | 2       |
| 5 | ledipasvir* OR GS-5885 OR GS5885 OR "WHO 9796" OR WHO9796   Completed   Studies With Results   updated from 02/04/2015 to  | 5       |

|    |   |    |
|----|---|----|
|    | 11/30/2015  |    |
| 6  | paritaprevir* OR veruprevir* OR "ABT 450*" OR "ABT450*"   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015                      | 0  |
| 7  | ombitasvir* OR "ABT 267" OR ABT267   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015   | 8  |
| 8  | dasabuvir* OR "ABT 333" OR ABT333   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015  | 7  |
| 9  | daclatasvir* OR "BMS 790052" OR BMS790052 OR "EBP 883" OR EBP883 OR Daklinza   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015 | 15 |
| 10 | asunaprevir* OR Sunvepra OR "BMS 650032" OR BMS650032   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015                        | 0  |
| 11 | grazoprevir* OR "MK 5172" OR MK5172   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015  | 0  |
| 12 | elbasvir* OR "MK 8742" OR MK8742   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015   | 0  |
| 13 | beclabuvir* OR "BMS 791325" OR BMS791325   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015                                     | 0  |
| 14 | GS5816 OR "GS 5816"   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015  | 0  |
| 15 | ABT-530 OR ABT530   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015  | 0  |
| 16 | Viekira OR Viekirax OR Exviera OR Holkira OR Harvoni   Completed   Studies With Results   updated from 02/04/2015 to 11/30/2015                         | 9  |
| 17 | or/1-16   | 80 |

### Search conducted by a Scientific Officer from the PGD project team

#### Grey Literature

Date of Search: November 20, 2015

Keywords: Hepatitis C, telaprevir, boceprevir, simeprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816 and ABT-530

Limits: From February 2015 to November 2015, English only

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching”

(<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)