Treatment for Hepatitis C Virus: a Systematic Review and Meta-Analysis

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Introduction

The hepatitis C virus (HCV) is a blood-borne viral infection that attacks the liver and can cause disease such as cirrhosis, liver failure and hepatocellular carcinoma[1]. It is estimated that 2.8% of the world's population[2] and 0.64-0.71% of Canadians have chronic hepatitis C (CHC)[3].

In approximately 25% of cases, individuals' immune systems spontaneously clear the virus and they no longer have the potential to develop HCV related liver disease, however individuals can be re-infected if re-exposed[4]. Many people with CHC are unaware that they are infected[5] and their blood can transmit the infection to others[1]. The virus is often only detected when individuals develop liver disease[6] for which severity may be affected by the age at which infection occurred, amount of alcohol use, diet and other lifestyle factors[5,7,8]. It is estimated that 80% or more of individuals with CHC will not suffer from severe disease such as cirrhosis after 20 years of infection[5,7,8].

Until 2011, the standard of care for CHC treatment in Canada was pegylated interferon alpha administered by injection plus oral ribavirin (PR)[9]. Since then, newer treatment regimens including direct acting antivirals (DAA) have received regulatory approval[1,9]. DAA-based treatment regimens (DAA-based regimens) have been found to improve sustained virological response (SVR)[9], which is characterised by an undetectable viral load at a pre-determined period of time after treatment (i.e. 12, 24 or 72 weeks). SVR is often used to measure treatment success because it has been shown to avert long term negative outcomes in many individuals[10]. In addition to improved SVR rates, there is evidence that these newer regimens have fewer side effects than PR alone and are less burdensome given they include oral components and are given for shorter treatment durations[11]. Some DAA-based regimens are also available without interferon (interferon-free), which has been shown to further reduce side effects[11].

Given that a separate systematic review on population based screening for HCV did not identify direct evidence on the effectiveness of screening[12], this systematic review and meta-analysis was produced for the Canadian Task Force on Preventive Health Care (CTFPHC) to inform the development of a clinical practice guideline which asks: What is the effectiveness of screening an asymptomatic population for hepatitis C?[13]. While most prior reviews have focussed on SVR as a proxy for treatment effectiveness, this review aims to directly compare older versus newer treatment regimens on additional patient important outcomes (e.g. hepatocellular carcinoma, hepatic decompensation, etc.).

The purpose of this systematic review is to examine the benefits and harms of newer (DAA-based) hepatitis C treatment regimens compared to older treatment (PR) regimens in treatment-naïve, non-pregnant adults. This review will be used as indirect evidence in deciding whether screening for HCV should be recommended in Canada. This review is not intended to replace reviews informing treatment regimens to recommend to patients.

Methods

Population, intervention, comparator, outcomes (PICO), outcome ranking, data sources and searches

This review is intended to provide indirect evidence on the value of population based screening. In an effort to more closely mimic treatment in an unscreened population, we included studies where over 80% of the participants were treatment-naïve and whose participants did not have HIV co-infection, a history of liver transplantation, hemodialysis, or occupational exposure[14] (Table 1, Figure 1).

The intervention was any currently available treatment approved for use in Canada and any emerging treatment regimens anticipated to become available in Canada by February 2016 (Table 2). We included all genotypes and our comparator was PR taken for 48 weeks.

The CTFPHC's HCV work group and a focus group of patients identified and rated outcomes[15]. The focus group was conducted by an independent research group, the Knowledge Translation Program based at St. Michael's Hospital, Toronto, Ontario. Patients included former or current intravenous drug users, individuals born between 1950 and 1970, individuals from countries with high HCV prevalence and individuals who were diagnosed with HCV[15]. All included outcomes were ranked by patients as being either critical or important.

The patient important outcomes (outcomes) included the following benefits: surrogate outcomes of reduced HCV transmission, sustained virological response and improvement in liver histology; and long term outcomes of reduced mortality (hepatic & all cause), hepatocellular carcinoma, hepatic decompensation, need for liver transplantation and improved quality of life. The harms comprised: withdrawal due to adverse events, psychological adverse events, neutropenia, flu-like symptoms, anemia and rash.

We updated the search strategy from a therapeutic review conducted by the Canadian Agency for Drugs in Technologies and Health (CADTH) in February 2015[9]. We used the AMSTAR[16] tool to critically appraise the methodological quality of the CADTH review (Appendix A). Included drugs were approved for use in Canada or had high likelihood of approval by February 2016 (Table 2). In addition to searching the databases identified by the CADTH[9] we also searched PubMed[17] and ClinicalTrials.gov[18] to November 18, 2015 and included all of CADTH's references[9] (included and excluded studies) for study selection. The full search strategies are provided in Appendix B. An updated search was conducted on November 18, 2016 by the Ottawa Evidence Review Synthesis Centre (Appendix C).

Study selection, extraction and quality assessment

Two reviewers independently screened abstracts and full texts of potentially relevant articles, extracted data from included studies and verified the accuracy and completeness of the other's data extraction. Conflicts were resolved by third party consultation. Included studies can be found in Appendix D and excluded studies can be found in Appendix E. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[19] can be found in Figure 2.

Our search identified randomised and non-randomised, controlled and uncontrolled interventional studies (including cost-effectiveness modelling studies (modelling)). However, to select the studies that were used to examine the impact of treatment on each outcome, following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[20] we used a staged approach starting from study types providing the highest quality evidence. For instance, we first searched for evidence on each individual

outcome from randomized controlled trials (RCTs) and if we found evidence from RCTs, then we did not search for evidence from any other study type. If evidence on a particular outcome could not be found from RCT data, then we searched for evidence from the following study types in sequential order: non-randomised controlled, non-randomized uncontrolled, then modelling studies.

Quality assessment involved two steps. First we critically appraised the methodological quality of all studies. RCTs were appraised using the Cochrane Risk of Bias tool[21] and modelling studies were evaluated using a CTFPHC modified Drummond checklist[22] and the CHEERS tool[23] (Appendix A). Upon consensus of the work group, we included the modelling study with highest methodological quality, and which reported on the greatest number of patient important outcomes by fibrosis score compared to the others (Appendix A). Next, we assessed the strength and quality of the body of evidence for each patient important outcome using the GRADE[20] approach (Appendix F).

Data synthesis and analysis

Risk ratios (RRs) and 95% confidence intervals (CIs) for benefits and harms of treatment were analysed in Cochrane Collaboration's Review Manager[24] and absolute effects were calculated as proportions per 1,000. In situations where there were no events in the control group, Review Manager automatically added 0.5 to each cell of the 2x2 table in order to allow for the calculation of RRs. Treatment at earlier versus later stages of fibrosis was also compared, where this data was available.

All data were processed with GRADEPro software[25] and presented in table format (Appendix G). Detailed methods can be found in the protocol[14] with outcomes and definitions available in Appendix H.
Due to the small sample size of some studies, particularly for sub-group analyses, the optimal information size (OIS) for each outcome was calculated and used to inform our GRADE assessments[26]. Optimal information size is based on a two-sided α=0.05 and desired power of 0.8, which was determined using this calculator: http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html[27].

The work group also established, a priori, clinical decision thresholds (CDT) for each patient important outcome, which dictated whether the clinical recommendation would be in favour or against treatment with DAA-based regimens (OIS and CDT, Appendix I).

Publication Bias

The small number of RCTs meant we could not assess for publication bias using funnel plots. Instead, we searched Clinicaltrials.gov[18] for registered protocols of studies not conducted (or reported on).

Indirectness of the Evidence

In addition to issues of indirectness in the study population mentioned above, drawing conclusions about the effectiveness of DAA-based regimens for a treatment naïve population are limited by the fact that we did not include studies that compared individuals who received treatment to those that did not. Such trials (not to be confused with delayed treatment studies) were not identified in our review of the literature likely because since the mid-1990s and the availability of PR as an effective treatment, these trials have not been conducted. It would be unacceptable to conduct a trial where individuals identified with HCV in the control group would not receive any treatment for HCV.

Results

Given the difference between our PICO (Table 1) and CADTH's[9], and our staged approach to study selection, a different set of studies emerged for inclusion and analysis in our review. Eleven publications[28-38] representing seven unique RCTs[28-32,36,37] and one modelling study[38] formed the evidence base for this review (Appendix J).

The RCTs[28-32,36,37] compared PR to various DAA-based regimens and reported on the following outcomes: SVR (12, 24, and 72 weeks), all-cause mortality, quality of life, anemia, flu-like symptoms, neutropenia, psychological adverse events, rash, and withdrawal due to adverse events. The mean age of participants was 45-55 years, with a slightly larger proportion of male participants; all were genotype 1 with the exception of one RCT[37] which included genotypes 1, 2 and 3. Participants had a wide range of fibrosis scores, were all HIV and hepatitis B negative and the majority (80% or more) were non-cirrhotic (Appendix D, Appendix K).

Despite conducting an exhaustive search for empirical evidence, we only identified modelling studies[6,38-40] reporting on the following outcomes: hepatic mortality, hepatocellular carcinoma, hepatic decompensation and need for liver transplantation. The selected model[38] simulates 1,000 HCV infected individuals to represent a cohort of 60 year old (in 2015) participants weighing 75 kg who are treatment-naïve, all genotype 1, but with a range of fibrosis scores (F0-F4) (Appendix D).

No studies were found reporting on the influence of treatment on developing cirrhosis, reduced HCV transmission, or improvement in liver histology.

Quality of the evidence

Following GRADE[20], results are presented by outcome based upon the quality of the evidence. Moderate quality means that the effect is likely to have occurred, low quality means there may be an effect, whereas very low quality means that it is likely that the estimate of effect is substantially different from the true effect. Complete results are available in the GRADE Evidence Profile tables which include the number of study participants, relative and absolute risks and quality ratings (Appendix G). Forest plots and risk of bias assessments are available in Appendix L.

Benefits

Compared to treatment with PR alone, individuals treated with DAA-based regimens are likely to achieve higher rates of SVR12, SVR24 and SVR72: 181 more (95% CI 137 more to 230 more)[RR 1.29 (95% CI 1.22, 1.37)], 190 more (95% CI 141 more to 239 more) [RR 1.31 (95% CI 1.23, 1.39)], and 215 more (95% CI 156 more to 281 more) [RR 1.36 (95% CI 1.26, 1.47)] per 1,000 patients treated, respectively. These results are based on RCT data rated as moderate quality, which in GRADE terms[20] means the effect is likely to have occurred.

Compared to treatment with PR alone, an interferon-free (sofosbuvir+ribavirin) regimen[37] showed no significant difference in SVR 12 [RR 1.01 (95% CI 0.89, 1.14)] and SVR 24 [RR 1.02 (95% CI 0.90, 1.16]. The single RCT did not include SVR 72. These results are based on a single low quality RCT[37] which included predominantly genotype 2 and 3 individuals. Low quality in GRADE terms[20] means there may not be a difference between the two regimens.

No differences in all-cause mortality [RR 2.14 (95% CI 0.23, 20.01)] (maximum 72 weeks follow-up)[28-31,37] (low quality evidence) and quality of life [based on a narrative review (Appendix F)] (120 weeks follow-up)[33-35] (very low quality evidence) were observed when comparing DAA-based regimens to PR alone.

A modelling study[38] comparing treatment with PR alone, to DAA-based regimens found the following benefits. (Appendix G):

- Hepatic mortality: 60 fewer modelled individuals per 1,000 (59 fewer to 62 fewer) [RR 0.45 (95% CI 0.44, 0.46)]
- Hepatocellular carcinoma: 18 fewer modelled individuals per 1,000 (17 fewer to 19 fewer) [RR 0.63 (95% CI 0.61, 0.65)]
- Hepatic decompensation: 46 fewer modelled individuals per 1,000 (46 fewer to 47 fewer) [RR 0.31 (95% CI 0.30, 0.32)]
- Need for liver transplantation: 4 fewer modelled individuals per 1,000 (4 fewer to 5 fewer) [RR 0.39 (95% CI 0.35, 0.42)]

These results are based on a modelling study[38] of very low quality and are therefore very uncertain, meaning that the estimate of effect likely differs substantially from the true effect.

Harms

Compared to treatment with PR alone, DAA-based regimens may reduce the frequency of the following harms associated with treatment[28-32,36,37]:

- Anemia: 42 fewer people per 1,000 (10 fewer to 69 fewer) [RR 0.83 (95% CI 0.72, 0.96)]
- Psychological adverse events: 30 fewer people per 1,000 (22 fewer to 37 fewer) [RR 0.68 (95% CI 0.61, 0.77)]
- Withdrawal due to adverse events: 35 fewer people per 1,000 (23 fewer to 41 fewer) [RR 0.30 (95% CI 0.17, 0.53)]

These results are based on RCT data[28-32,36,37], which was rated as low quality and in GRADE terms[20] this means the effect may have occurred.

Compared to treatment with PR alone, we found that treatment using an interferon-free DAA-based regimen (sofosbuvir+ribavirin)[37] may provide further reductions in the frequency of harms associated with treatment:

- Flu-like symptoms: 154 fewer people per 1,000 (121 fewer to 168 fewer) [RR 0.15 (95% CI 0.07, 0.33)]
- Neutropenia: 121 fewer people per 1,000 (93 fewer to 121 fewer) [RR 0.02 (95% CI 0.00, 0.25)]
- Rash: 87 fewer people per 1,000 (32 fewer to 120 fewer) [RR 0.51 (95% CI 0.32, 0.82)-]
- Psychological adverse events: 46 fewer people per 1,000 (36 fewer to 53 fewer) [RR 0.44 (95% CI 0.35, 0.56)]
- Withdrawal due to adverse events: 107 fewer people per 1,000 (81 fewer to 116 fewer) [RR 0.10 (95% CI 0.03, 0.32)]

These results are based on data from a single RCT[37] which was rated as low quality and in GRADE terms[20] this means the effect may have occurred.

Summary of key benefits and harms

In summary, DAA-based regimens provide significantly greater benefits in surrogate outcomes (SVR 12, 24 and 72) and provide a reduction in the frequency of harms associated with treatment (anemia, psychological adverse events, withdrawal due to adverse events), compared with PR alone. In addition, using an interferon-free DAA-based regimen (sofosbuvir+ribavirin) provides an even larger reduction in the frequency of some treatment related harms (flu-like symptoms, neutropenia, rash, psychological adverse events, withdrawal due to adverse events). Based on very low quality modelling data, our review found that DAA-based regimens could be preferable to treatment with PR alone to reduce long term outcomes of hepatic mortality, hepatocellular carcinoma, hepatic decompensation, and need for liver transplantation.

Treatment at earlier versus later fibrosis stages

Based on two moderate quality RCTs[30,31] reporting on SVR12 when comparing treatment regimens to each other (i.e. PR with PR, DAA with DAA) the studies reported improved rates of SVR with early treatment (F0-F2) compared with later (F3-F4) treatment (Appendix N). Similarly, based on one low quality RCT[28] for the outcomes of SVR 12 and 24, the authors reported a pattern of improved rates of SVR with early treatment (F0-F2) compared with later (F3 only) treatment. Specifically, all three RCTs reported a greater percentage of individuals achieving SVR when treated earlier versus later, however statistical tests were not performed on any of these results.

Pertaining to three long term outcomes (hepatic mortality, hepatic decompensation and need for liver transplantation)[38], clinical benefits in modelled individuals may be approximately doubled if treatment is initiated at an earlier (F0-F3) stage of fibrosis versus later (F4 - cirrhosis). For example when comparing PR with DAA-based regimens, if 1,000 modelled individuals with F0-F3 are treated, approximately 60 fewer modelled individuals might die from hepatic mortality versus 30 fewer if treated at stage F4 (with cirrhosis). These findings should be interpreted with caution given the very low quality of the evidence and high uncertainty associated with the estimates.

Interpretation and Discussion

The main purpose of this review is to inform the upcoming CTFPHC's guidelines on screening for HCV[13]. This review provides the CTFPHC with indirect evidence showing that treatment regimens for HCV (both PR and DAA-based regimens) are effective in helping patients (not identified through screening) to achieve SVR (Appendix O), with DAA-based regimens achieving higher SVR rates (after 24 weeks up to 91% of patients had achieved SVR) (Appendix O), and producing fewer harms (e.g. serious and non-serious adverse events related to treatment) for patients. Currently the College of Family Physicians of Canada/Public Health Agency of

Canada 2009 guidelines[41] recommend in favour of screening high-risk groups for HCV. If the CTFPHC were to recommend screening more broadly across Canada (e.g. population screening or birth cohort screening), this would result in an increase in treatment uptake. If this were the case, clinicians and policy-makers may wish to consider the use of DAA based regimens, and preferably interferon-free DAAs, instead of PR for treating these individuals. Due to the lower risk of harms and adverse events, the use of DAA based regimens (in particular interferon-free DAAs) is likely to result in increased treatment adherence by patients.

Approximately 16% of people with CHC develop cirrhosis at 20 years and 41% at 30 years[11], which means that a high percentage of affected individuals will never go on to develop end stage liver disease despite not being treated. Therefore, although, our findings show that new DAA-based treatment regimens are highly effective in achieving SVR with relatively small harms involved for patients, overtreatment continues to be of concern. There is a lack of evidence examining the effectiveness of screening and the risks of overtreatment. This needs to be considered when policy makers are making decisions on population based screening and treatment thresholds. In addition, feasibility and acceptability must also be addressed, including the high cost of drugs for treatment.

This review differs from previous systematic reviews in terms of its scientific rigour. While we based our main conclusions on RCT evidence, in Canada the latest CADTH[9] review, which also examined the effectiveness of treatment, included non-randomised studies with no comparator, and those with historical controls in their body of evidence, and conducted indirect comparisons through a network meta-analysis to determine the effectiveness of the different treatment regimens[9]. Non-randomised studies are more prone to bias, including selection bias, which can lead to more optimistic results[21]. Another relevant review is the World Health Organization's 2014 systematic review and meta-analysis[42] which, like the CADTH review[9], included single arm trials with no controls. The authors used historical controls instead to conduct the comparisons and determine the effectiveness of new treatment regimens. Similarly, the United States Preventive Task Force (USPSTF) based its findings related to achievement of SVR on 19 cohort studies and not RCTs[43]. In contrast to these three reviews[9,42,43], our review included RCTs with direct comparisons between treatment regimens (PR versus DAA-based regimens), which allowed us to conduct a meta-analysis of the data. By including a meta-analysis, we were able to increase our statistical power and develop more precise conclusions regarding the benefits and harms of treatment[21]. In the future, studies on newer treatment regimens should consider the use of a RCT design (versus single-arm trials) in order to allow for the direct comparison of treatment regimens and robust meta-analyses. Studies that directly compare the long term benefits and harms of HCV screening would also be beneficial, including those evaluating improvements in liver histology, developing cirrhosis, and rates of HCV transmission.

Strengths and Limitations

This review and meta-analysis is a direct treatment comparison based on explicit inclusion and exclusion criteria, which utilised PR as a comparator. We followed a rigorous systematic review development process including two reviewers screening studies and completing data extraction. By implementing a staged approach starting from study types providing the highest quality evidence, the evidence for the majority of our outcomes (n=8) was based on RCT data[28-32,36,37]. The HCV work group of the CTFPHC and a focus group of patients rated patient important outcomes. We applied a rigorous approach to quality assessment using the GRADE approach[20].

The use of CADTH's search strategy[9] and limiting to English language studies may have limited the body of evidence. Since our review identified RCTs that used PR as a comparator, we did not include single arm trials

(with or without historical controls as a comparator), which limited the number of DAA treatment regimens which were included in the review. Our search did not identify RCTs, non-randomised controlled, non-randomised uncontrolled studies (including single-arm and non-PR controlled studies) reporting on four long term outcomes; therefore we included a modelling study, which constituted very low quality evidence, to inform those outcomes. The model itself is based on many assumptions and it is unclear whether or not its results would be seen in real-world clinical practice. By including individuals who were diagnosed with HCV in our patient sample for rating of outcomes, we may have introduced bias as some of these individuals would likely not be representative of an asymptomatic population as outlined in our PICO.

Conclusion

Treatment regimens for HCV (both PR and DAA-based regimens) are effective in helping patients (not exclusively identified through screening) to achieve SVR. DAA-based regimens achieve higher SVR rates and produce less harms than PR. Interferon-free DAA-based regimen may further reduce the harms associated with treatment. Compared to PR alone, DAA-based treatment regimens might further reduce the risk in patients to develop hepatic mortality, hepatocellular carcinoma, and hepatic decompensation, and reduce the need for liver transplantation.

Registration
The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on (November 24, 2015) (CRD42015029513)

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Contributions

Francesca Reyes Domingo and Alejandra Jaramillo Garcia contributed substantially to the study concept and design; Francesca Reyes Domingo was responsible for the data analysis and Francesca Reyes Domingo, Alejandra Jaramillo Garcia, Nathalie M. Holmes, Rana Rahal, Mitulika Chawla and Kristin Klein contributed to the interpretation of the data. All of the authors reviewed and rated the studies. All of the authors drafted the manuscript and revised it critically for important intellectual content. All of the authors gave final approval of the version to be published and agreed to act as guarantors of the work.

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Figure 1. Analytical Framework

The analytical framework includes the population, the intervention and the patient important outcomes of interest to answer the CTFPHC's question on screening for HCV. Items in bold boxes represent key questions 1 & 2 in this review and correspond with KQ6 & KQ7 respectively found in the analytical framework[13] include relevant patient important outcomes.

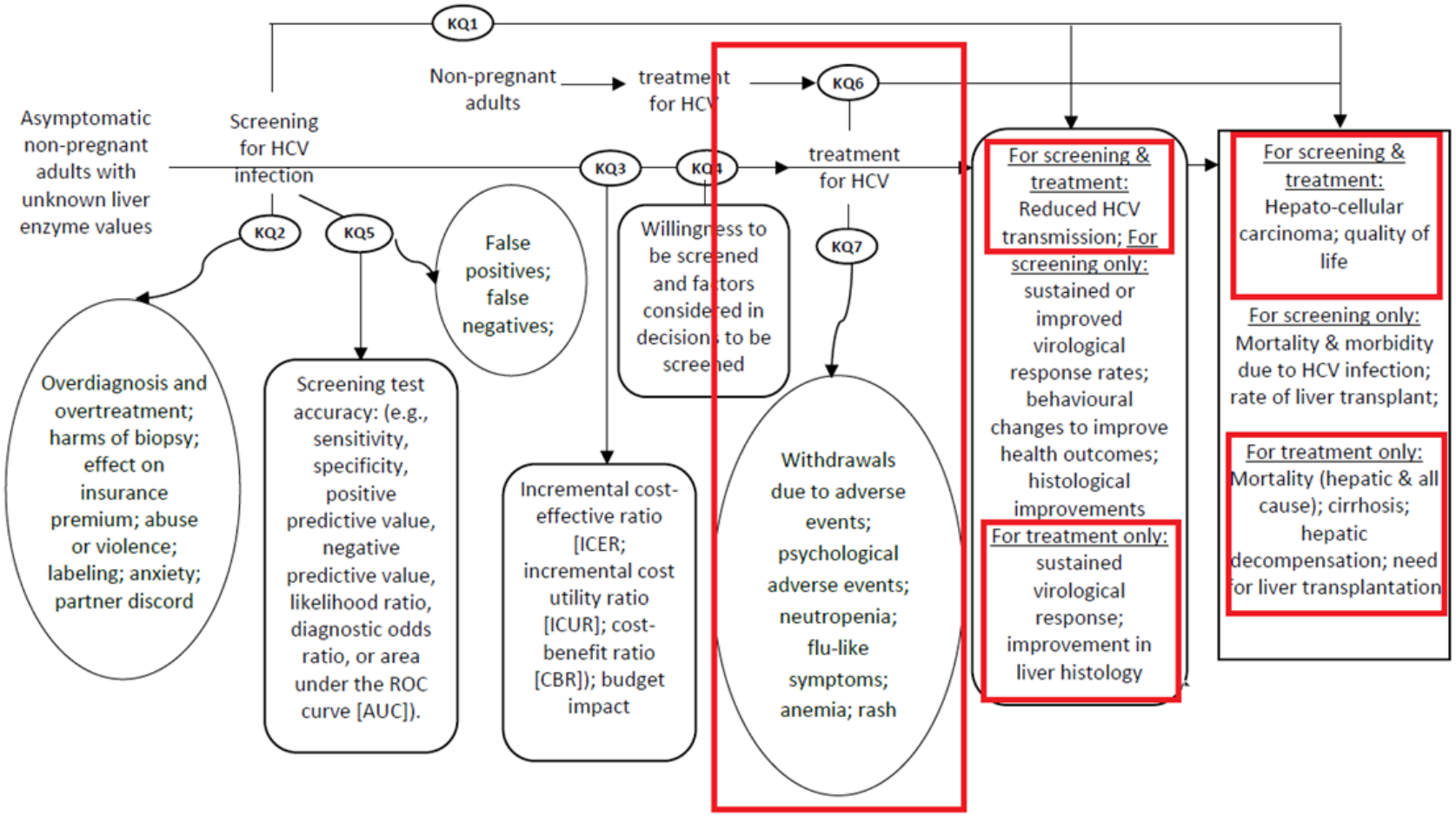


Figure 2 - Study selection (PRISMA) flow chart[19]

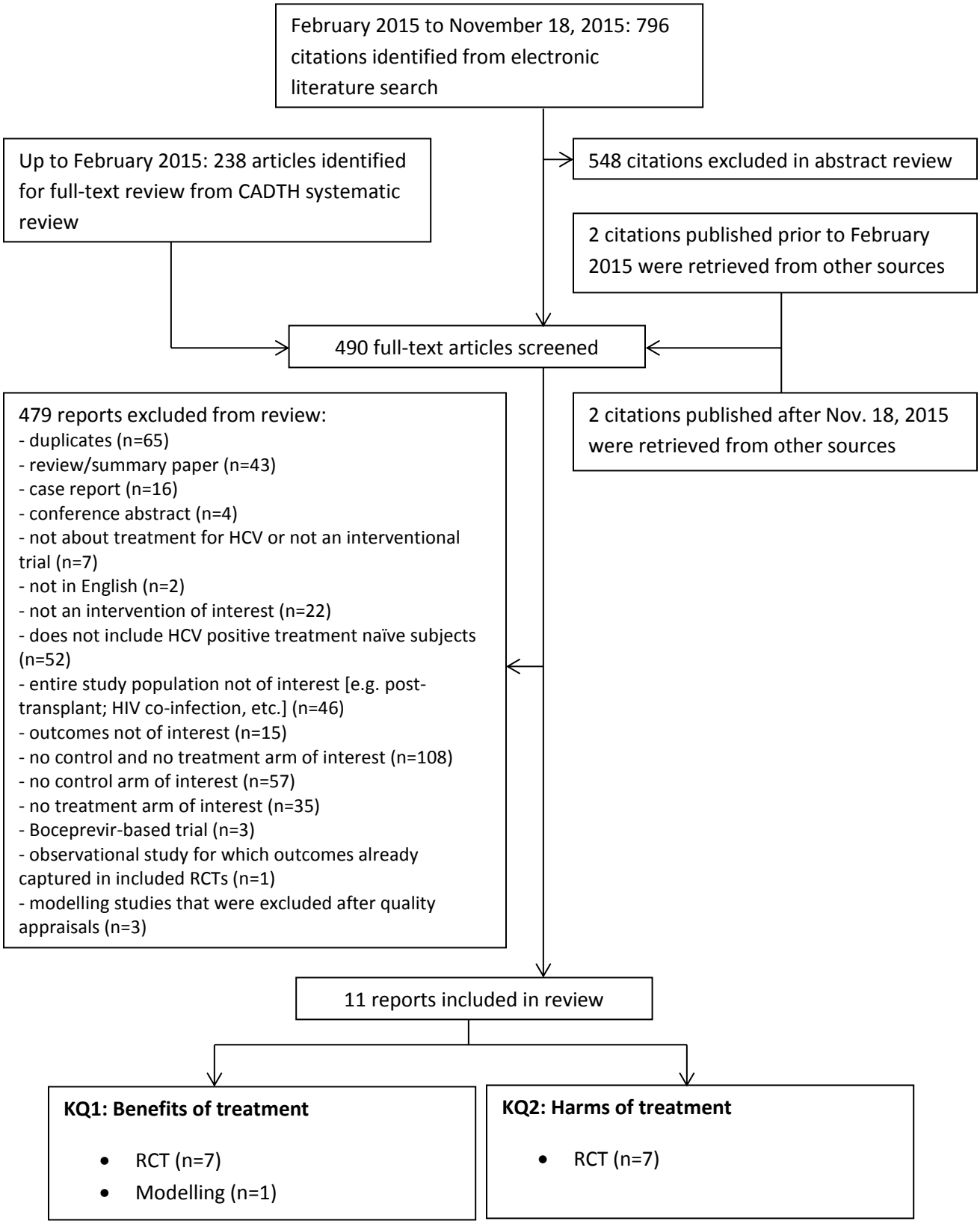


Table 1

Inclusion and Exclusion Criteria- Treatment questions (KQ1 and KQ2); Population, Intervention, Comparator and Outcome (PICO)[14] Table

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?

	Inclusion	**Exclusion**
Population	Treatment-naïve non-pregnant adults without exclusion criteria representing a minimum of 80% of the study population	Post-transplant patients; people with human immunodeficiency virus (HIV); hemodialysis patients; people with occupational exposure
Interventions	Any currently available treatment approved for use in Canada and any emerging regimens anticipated to become available in Canada by February 2016 for HCV of all genotypes (1-6)	
Comparators	KQ1: PR48 (Pegylated interferon plus ribavirin for 48 weeks)	
Patient Important Outcomes	KQ1: Benefits Long-term outcomes: mortality (hepatic & all cause), Cirrhosis, hepatocellular carcinoma, hepatic decompensation, need for liver transplantation, quality of life (all scales reported). Surrogate outcomes: reduced HCV transmission, sustained virological response, improvement in liver histology. KQ2: Withdrawal due to adverse events, psychological adverse events, neutropenia, flu-like symptoms, anemia, rash	
Settings	Settings where treatment for HCV is commonly or may be performed (e.g., specialised centers)	
Study designs	For study selection, a staged approach starting from study types providing the highest quality evidence was used for each outcome starting with randomised or non-randomised, controlled or uncontrolled, interventional studies including cost-effectiveness economic modelling studies.	
Language	English	
Search timeframe	Limited to earliest time frame available in each database to November 18, 2015.	

Table 2

Treatment Regimens

This systematic review and meta-analysis categorises the treatment regimens into two groups: older "dual therapy" (PR) and newer Direct Acting Antiviral treatment regimens (DAA-based regimen) which include interferon-free DAAs. All of the included RCTs compared PR with DAA-based regimens. This review only identified one RCT, which included an interferon-free DAA treatment regimen: sofosbuvir+ribavirin and the modelling study primarily modelled interferon-free DAA treatment regimens. The following are the various treatment regimens listed by study type. <u>RCTs:</u> PR Simeprevir+PR Sofosbuvir+PR Sofosbuvir+ribavirin (interferon-free) <u>Modelling study:</u> PR Sofosbuvir+PR Sofosbuvir+simeprevir (interferon-free) Sofosbuvir+ledipasvir (interferon-free) Sofosbuvir+ribavirin (interferon-free) Ombitasvir/paritaprevir/ritonavir+dasabuvir ± ribavirin (interferon-free)
The following treatment regimens were eligible for inclusion in this review; however our search did not identify studies which met our selection criteria for these regimens: Elbasvir+grazoprevir Simeprevier+sofosbuvir Simeprevier+sofosbuvir+ ribavirin Sofosbuvir+velpatasvir (GS-5816)±ribavirin Sofosbuvir+ledipasvir+ribavirin
Based on consensus of the working group, the following treatment regimens were excluded from this review due to being discontinued for use in Canada. Boceprevir+PR Telaprevir+PR

Appendix A

Detailed Critical Appraisal of Included Studies

A) AMSTAR[16] Assessment Results - CADTH therapeutic review, drugs for chronic hepatitis C infection: Clinical review[9]

AMSTAR is a measurement tool created to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

- ✓ Yes
- No
- Can't answer
- Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

- Yes
- ✓ No
- Can't answer
- Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

- ✓ Yes
- No
- Can't answer
- Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

- ✓ Yes
- No
- Can't answer
- Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

- ✓ Yes
- No
- Can't answer
- Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

- ✓ Yes
- No
- Can't answer
- Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

- ✓ Yes
- No
- Can't answer
- Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

- ✓ Yes
- No
- Can't answer
- Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

- ✓ Yes
- No
- Can't answer
- Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

- Yes
- ✓ No
- Can't answer
- Not applicable

11. Was the conflict of interest stated?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

- Yes
- ✓ No
- Can't answer
- Not applicable

Overall Score = 8/11

B) Cochrane Risk of Bias[20] Results for RCTs

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Fried 2013[28], The Randomized PILLAR Study	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Hayashi 2014[29], CONCERTO-1 trial	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Jacobson 2014[30], QUEST-1	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Lawitz 2013-1[36], FISSION trial	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
Lawitz 2013-2[37], NCT01188772 trial	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Manns 2014[31], QUEST-2 trial	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NCT01725529 2015[32]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
Scott 2014[33]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
Wei 2016[34]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
Younossi 2014[35]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk

C) Quality Appraisal of Modelling Studies - Drummond[22] short tool

Quality Appraisal of the Economic Studies					
	Question	**Wong 2015[6]**	**Gissel 2015[40]**	**Dan 2015[39]**	**Chahal 2015[38]**
Drummond	**1.** Was a well-defined question posed in answerable form?	Somewhat vague –"We developed a state-transition model of HCV to assess the cost-effectiveness of alternative screening strategies for patients with chronic HCV mono-infection in Canada."	Yes, clear objective: "two treatment regimens for genotype 1 infection received conditional approval in the European Union…We aim to analyze the cost-effectiveness of both regimens in Germany."	Not a question but a clear objective: This study aims to project the long-term reduction of liver complications and cost-effectiveness of treatment strategies, including co-administered BOC with PR compared with PR.	Yes, clear objective: To assess the cost-effectiveness of (1) treating all patients with HCV vs. only those with advanced fibrosis and (2) treating each stage of fibrosis.
Drummond	2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	Yes	Yes - SOF + RBV for 24 weeks and SOF+SIM with or without RVB for 12 weeks	Yes: BOC+PR vs. PR	Yes: PR48 SOF+PR SOF+RVB SOF+SIM SOF+LDV 3D+RVB
Drummond	**3.** Was the effectiveness of the programme or services established?	Yes	Yes	Yes	Yes
Drummond	4. Were all the important and relevant costs and consequences for each alternative	Yes – we are assuming they chose the correct values	Yes, did a PubMed search for 'hepatitis c cost Germany' and used 2 studies that reported German costs which	Yes – we are assuming they chose the correct values; NOTE: potential difference with Canada: In Singapore PR are	Yes – we are assuming they chose the correct values

	identified?		were converted to 2014 Euros (€). Drugs based on Lauer-Taxe which reports drug costs in Germany. Some costs are expected to be different in Germany than Canada.	packaged free with no cost to the payer when patients are taking BOC with PR.	
Drummond	**5.** Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, and gained life years)?	Yes	Yes	Yes	Yes
Drummond	**6.** Were the cost and consequences valued credibly?	Yes	Yes	Yes	Yes
Drummond	7. Were costs and consequences adjusted for differential timing? 7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate	Yes, future costs and health benefits were discounted at 5% annually, but no rationale given	Yes, costs were discounted by 3% according to German Institute for Quality and Efficiency in Health Care but no rationale given	Yes, costs were discounted by 3% for the base case, 0% for the lower case and 5% for the upper case, but no rationale given	Yes, costs were discounted by 3%, but no rationale given

	used?				
Drummond	**8.** Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes	Yes	Yes
Drummond	**9.** Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes, had lower and upper limits for costs of AEs/ long term complications, but one cost for drugs	Yes, they used lower case/upper case and provided a base case with CIs	Yes, had lower and upper limits
Drummond	10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes	Yes	Yes

D) Quality Appraisal of Modelling Studies - Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[23]

Quality Appraisal of the Economic Studies using CHEERS					
		Wong 2015[6] Analysis based on Study and Appendix 2: Detailed Methodology	**Gissel 2015**[40]	**Dan 2015**[39]	**Chahal 2016**[38]
Title and abstract					
1) Title	Title - Identify the study as an economic evaluation, or use more specific terms such as ''cost-effectiveness analysis'' and describe the interventions compared.	Partial. Cost-effectiveness of screening for hepatitis C in Canada Does not indicate interventions	Yes. Cost-effectiveness of INF-free therapy for Hepatitis C in Germany - an application of the efficiency frontier approach	Yes. Cost-effectiveness of BOC co-administration versus PEG alpha-2b and RBV only for patients with hepatitis C genotype 1 in Singapore	Yes. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population
2) Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	No. Missing key information such as sensitivity, discount rate and perspective	No. Missing key information such as sensitivity and discount rate	No. Missing key information such as sensitivity, discount rate and perspective	No. Missing key information such as discount rate and perspective
Introduction					
3) Background and objectives	Provide an explicit statement of the broader context for the study. Present	Yes, Page 1	Yes, Page 1	Yes, Page 209	Yes, Page 66

	the study question and its relevance for health policy or practice decisions.				
Methods					
4) Target population and subgroups	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.	Yes, chronic HCV mono-infected patients in Canada based on 2011 census Onetime screening for individuals aged 25–64 or 45–64 Rationale: United States' birth cohort screening (1945-1965)	Yes, the most important baseline characteristic of simulated patients is the degree of fibrosis according to the METAVIR scoring system using 4 treatment regimens Rationale: not explained	Yes, treatment naïve patients, who had failed prior treatment. Sub-group analyses: non-cirrhotic treatment experienced patients and null responders Asian population represented by Singapore. Rationale: not explained	Yes, a cohort of treatment-naïve 60-year-old patients (birth year,1955) weighing 75 kg who are aware of their HCV infection Rationale: Based on data from the 2010 National Health And Nutrition Examination Survey, indicating that 70% of HCV infected persons were born from 1945 to 1965
5) Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes, screening and treatment at Canadian tertiary care hospital. Estimates from Payer perspective and Toronto Western Hospital, University Health Network used to estimate the health and economic effects of various screening and treatment strategies for chronic HCV infection in Canada.	Yes, for use in clinical practice in German as regulated by German Statutory Health Insurance and the German Institute for Quality and Efficiency in Health Care.	Yes, unsubsidized cost of liver-associated health status collected from National University Hospital, Singapore (NUHS) (major referral center). Cost data collected from NUHS makes the result of this study a good reference from public perspective. Asian population represented by Singapore. As the licensing label for BOC in Singapore is different from the clinical trial design, therefore the treatment-related inputs were based on a post hoc analysis from clinical trials.	Yes, despite clinical practice guidelines recommending the new antiviral drugs, some payers require a higher level of fibrosis before authorizing treatment. Untreated chronic HCV infection can progress with increasing fibrosis, reaching cirrhosis in 20% to 30% of patients, and related liver complications, including premature death, in a smaller subset. Even with viral elimination, some patients may experience disease progression. Earlier treatment might provide important clinical and cost benefits.
6) Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.	Yes, Canadian payer perspective structured as a cost–utility analysis, with outcomes expressed in terms of QALYs and costs.	Yes, short-term and long-term costs and benefits from perspective of German Statutory Health Insurance. Used efficiency frontier method, which was suggested by German Institute for Quality and Efficiency in Health Care	Yes, payer and public perspective, actual real life costs used which make it applicable to both. Outcomes expressed as QALYs.	Yes, they adopted a societal perspective, including all direct medical costs for HCV management and therapy. For each cycle, the patients accrued corresponding costs and QALYs of the health state over a lifetime.

			(not QALY).		
7) Comparators	Describe the interventions or strategies being compared and state why they were chosen.	Yes. Age 25-64 and 45-64. No screen. Screen & Treat PR. Screen & Treat INF-free DAA (G1), SOF+RBV (G2/3) or PEG IFN+RBV (G4/5/6). Screen & Treat SIM+ PEG IFN+RBV (G1), SOF+RBV (G2/3) or PEG IFN+RBV (G4/5/6).	Yes. PR, BOC+PR, SOF/RBV, SOF/SMV.	Yes. PR, BOC+PR	Yes. By treatment regimen: 1)No Treatment 2)PR 48 3)SOF/PR 12 4)SOF/R 24 5)SIM/SOF 12/24 6)SOF/LDV 8/12 7)SOF/LDV 12 8)Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (3D) ± RBV. * Treat All vs. treat at F3/F4with each of the seven therapy options * Treatment by Fibrosis Stage
8) Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes, Lifetime Page E114	Yes, Lifetime Page 297	Yes, Lifetime Page 210	Yes, Lifetime Page 165
9) Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes, future costs and health benefits were discounted at 5% annually, based on Guidelines for the economic evaluation of health technologies: Canada, CADTH.	Yes, all costs used in the model are in 2014 Euros and were discounted by 3 %, as suggested by German Institute for Quality and Efficiency in Health Care.	Yes, discount Rate Base 3%, Lower 0%, Upper 5%. Could not identify reason in paper.	Yes, discount rate 0.03 (0.01-0.05) as a means of comparison.
10) Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes, QALYs	Partial, do not use QALYs, but German IQWIG and SVR rates	Yes, QALYs	Yes, QALYs
11) a. Measurement of effectiveness	Single study–based estimates: Describe fully the design features of the single effectiveness study	N/A	N/A	N/A	N/A

	and why the single study was a sufficient source of clinical effectiveness data.				
11) b. Measurement of effectiveness	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	Yes, used baseline analysis of deaths prevented and QALY gained Disease parameters from a systematic review. Transition probabilities to advanced liver disease obtained from a published study. Mortality rates for advanced liver disease from a US study based on cancer registries.	Yes, used costs and efficiency frontier to measure additional percentage point of SVR gained Treatment simulated for the duration per German Society for Gastroenterology, Digestive (DGVS) and Metabolic Diseases guidelines. All-cause mortality applied according to German life tables. Modeling characteristics were adapted to reflect clinical practice in Germany. Effectiveness analysis is based on German Federal Joint Committee assessment for PR & BOC. For SOF use a single trial.	Yes, used QALYs from higher rates of SVR and lower costs from avoidance of complications Efficacy, and compliance were based on two trials. Distribution of fibrosis stages also based on two trials. Inputs related to all-cause mortality rate and treatment costs were specific to Singapore.	Yes, likelihood of SVR and treatment discontinuation were determined by meta-analyses of phases 2 and 3 clinical trials. Natural history of disease and SVR rates also from meta-analysis, but linkages between SVR rates and long-term outcomes based on single studies.
12) Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes. [How did they come up with the utility values used in relation to the health states (QALY)?]	Yes, they obtained utility data health states from the most recent Canadian utility study available: Hsu et.al 2012 and based on the Health Utilities Index Mark 2. That study included 700 patients across different chronic HCV infection health states.	N/A Not applicable as this study does not use QALY, but IQWIG. The study states: IQWIG suggested to aggregate specific efficiency frontier results based on patient preferences as found by analytic hierarchy processes or conjoint analyses. Aimed to analyze whether the problems outlined above prevent useful results if the	Partial. The utility inputs are derived from two studies however one study (Siebert et al.) references another study's results.	Yes, the utility values were determined from a literature review.

			efficiency frontier method is applied to DAAs for HCV in Germany.		
13) a. Estimating resources and costs	Single study–based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Partial Yes, CHC-related costs were collected from a large Canadian costing study using administrative data and based on Toronto Western Hospital, University Health Network to estimate the health and economic effects of various screening and treatment strategies to apply. The costs of antiviral therapies were collected from common drug review reports. The cost of screening was based on the Ontario Health Insurance (OHIP) Schedule of Benefits and Fees.	N/A	Partial. Used the CHOosing Interventions that are Cost Effective from WHO suggests using three times of GDP per capita as the threshold for cost-effectiveness. They used the absolute GDP as threshold for highly cost-effective treatment strategy. The unsubsidized cost of liver-associated health status was collected from National University Hospital. Pharmaceutical and health status costs obtained from a public hospital in Singapore.	Partial, pages 12-19 of the supplemental information provides all the input parameters used for the model which are numerous. Use of parameters and costs are based on German clinical practice and German Federal Joint Committee report.
13) B. Estimating resources and costs	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	Yes, they searched Pubmed for 'hepatitis c cost germany' to adapt the model to German prices.[Could not identify how they adapted] Out of 65 hits, only 2 studies could be identified as reporting original German cost data for HCV. All drug costs reflect German prices as of August 2014 (according to Lauer-Taxe).[LT is a document listing all drug prices in Germany]	N/A	N/A
14) Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated	Yes, non-Canadian cost data were converted to Canadian dollars at the purchasing power parity conversion rate. All cost data were inflated to 2012 using the Statistics Canada Consumer Price Index for health care and personal items.	Yes, all costs used in the model are in 2014 Euros [Included studies are from different years 2013/2006. Could not find what exchange rate was used]	No, could not find how they converted the costs	No, costs are in US dollars adjusted to 2014 using the medical component of the US Consumer Price Index.

	unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.				
15) Choice of model	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	Partial. Used a state-transition model including both Markov model cohort simulation as well as individual-based (first-order Monte Carlo) microsimulation. http://mdm.sagepub.com/content/32/5/690.full] Figure 1 provides a flow diagram. But did not state why chose model	Partial. The model analyzes both short-term and long-term costs and benefits from the perspective of the German Statutory Health Insurance. Applied the efficiency frontier method, which was suggested by German Institute for Quality and Efficiency in Health Care (IQWIG) for cost-effectiveness analysis in Germany. But did not state why chose model.	Yes. A Markov model was developed to capture the disease progression and project the lifetime cumulative incidence of advanced liver-related complications (decompensated cirrhosis, hepatocellular carcinoma) and liver transplant, in order to be consistent with current understanding of the biology of chronic HCV-related liver disease and associated treatment Do not provide a flow diagram structure	Yes. Constructed a decision-analytic model of HCV to examine the clinical outcomes and costs of treatment initiated at different disease stages. Intent is to portray societal costs, as approximated by the cost of care sources on which we rely. Owing to the imprecision of unit cost inputs and the greater uncertainty introduced by estimated rates of patients under current care and use of health care resources, we examined wide ranges of costs in sensitivity analyses. eFigures 1-3 in the supplemental information show the model structures.
16) Assumptions	Describe all structural or other assumptions underpinning the decision-analytic model.	Individuals offered one-time screening through primary care physician at regular visit ("case finding") strategy. Screening is a blood test for HCV antibody. All positive tests followed by an HCV RNA test to confirm infection. Model assumes all who test positive referred to a hepatologist /gastroenterologist/ infectious disease specialist and may be offered treatment with PR according to the Canadian guidelines.	Used SVR to define treatment success. Early benefit assessments of SOF and SMV by German Federal Joint Committee defined both PR and triple therapy with first generation (BOC or TEL) as appropriate comparators. Modelled cost-effectiveness of comparators and the two IFN-free therapies with an extended Markov model since it was also used for	Used a small patient sample size which makes comparing groups not statistically significant, but also reflects their understanding and assumption that even with successful SVR in decompensated cirrhotic patients, progression to HCC or liver related death due to portal hypertension may still occur. Considers that Asian ethnicity has a higher incidence of IL28B genotype that makes Asians more responsive to standard therapy. Second part of analysis adjusted response rate based on	Assumed that patients who achieve SVR have no risk for reinfection with HCV, thus tending to overestimate cost effectiveness. Does not consider extended treatment for patients with slow responses or the repeated treatment of patients who do not achieve SVR. Uses aggregated annualized transition probabilities to simulate progression from one clinical state to the next,

			analysis in the United Kingdom and in Japan which reflects the relatively slow progression. All modeling characteristics adapted to reflect clinical practice in Germany.[but don't say how in paper]	published meta-analysis on prevalence of favourable IL28B. Since patients more likely respond to triple therapy earlier than traditional treatment, the increased cost of BOC can be offset by the shortened duration of treatment.	adjusted for age but not for other individual traits. Individual heterogeneity in CHC progression is represented by varying progression rates in sensitivity analyses Analysis took into account only direct medical costs, omitting potential gains in productivity.
17) Analytic methods	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Conducted the base-case analysis (the state transition model) to estimate the expected value using deterministic calculations. Then ran a full deterministic one-way sensitivity analysis on all model's parameters over the plausible ranges using the reported 95% confidence interval (CI) ranges. Finally they ran probabilistic sensitivity analyses using the Monte Carlo simulation for 5,000 iterations for all three screening strategies.	[Could not find this in paper but did conduct a robust sensitivity analysis]	The lower and upper values of clinical inputs and utility values are referred to the bounds of 95% confidence interval, while the values of health status cost are estimated as 25% lower and higher compared to the baseline value. All input values for sensitivity analysis are summarized in Table 1. [Conducted a robust sensitivity analysis]	They conducted 1-way sensitivity analysis on each variable to determine effects on the ICER and 2-way sensitivity analysis on selected variables. The aggregate uncertainty from multiple inputs was quantified via probabilistic sensitivity analysis using uniform distributions. The range in input values was determined by 95% CIs from primary literature sources or meta- analyses. When such data were unavailable, they varied the base case value from 50% to 150%.
Results					
18) Study parameters	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate.	Yes, validated against published results for natural history part of the model using baseline parameter values and compared the prediction of model to external studies. Disease progression parameters were obtained from a systematic review which estimated the annual transition probabilities between fibrosis stages from 111 prognostic studies including 33,121 patients. Transition probabilities to advanced liver disease obtained from a published study which provided separate estimates for both SVR and non-SVR CHC patients. Mortality rates for advanced liver disease obtained from a US study and	No, does not appear validated against published results. They reference two Markov models on one used in United Kingdom and in Japan. Both models are industry funded and neither model appears to have been externally validated.	No, does not appear validated against published results. They referenced model appears to have been validated. They have been completed by mostly same authors and are funded by industry.]	Yes, validated against published results by comparing predictions with the results of empirical natural history studies and prior models. Further information is available in supplementary information.

	Providing a table to show the input values is strongly recommended.	a systematic review. An input table is provided in the paper.			
19) Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes, table 3 in the paper includes ICERs for all interventions as well as the cost differences between the different groups.	Partial, the outcomes of cost-effectiveness analyses with the efficiency frontier approach are maximum reimbursable prices. Under current German legislation, no cost-effectiveness analysis is involved in the process of the initial rebate negotiations. No ICERs calculated.	Yes, the ICER does vary and part of minimum and maximum values are summarized in Supplement Material C. Tables 2, 3 & 4 also include ICERs for all interventions as well as the cost differences between the different groups.	Yes, ICER values are provided with a range (lower and upper limit) and values based on varying sensitivity analyses are also provided. These can be found pages E4-E6 of the report and in Sections III & IV of the supplemental information.
20) a. Characterizing uncertainty	Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	N/A	N/A	N/A
20) b. Characterizing uncertainty	Model-based economic evaluation: Describe the effects on the results of	They performed both 1-way deterministic sensitivity analyses and probabilistic sensitivity analyses, using the same assumptions as the base-case analysis, to explore the effect of uncertainty of the model's parameters. For the deterministic sensitivity analyses see Appendix 7 &8 which summarize the	They performed a multivariate probabilistic sensitivity analysis. Parameter estimates were varied within the uncertainty	The sensitivity analysis were conducted with clinical inputs, cost of health status, and utility values corresponding to the quality of life, in order to compare the cost and benefit between two	They conducted 1-way sensitivity analysis on each variable to determine effects on the ICER and 2-way sensitivity analysis on selected variables. The

	uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	effects of varying the parameters related to chronic HCV infection, to screening and to treatment, with use of tornado diagrams to examine the cost-effectiveness of screening.	distributions that best reflect the nature of each specific parameter. Uncertainty margins are applied to each input parameter of interest based on corresponding intervals provided in the literature or based on assumptions if information was unavailable. The standard error was assumed to vary 20 % around the mean in case information on variance was not available for a specific parameter applied to German cost data. Details in Table 1 & 2.	treatment schemes. In order to simulate the results of inputs change due to exogenous causation, they took the uncertainty of clinical input (i.e. transition probabilities between different stages of liver complication), utility and treatment cost into consideration. The lower and upper values of clinical inputs and utility values are referred to the bounds of 95% confidence interval, while the values of health status cost are estimated as 25% lower and higher compared to the baseline value. All input values for sensitivity analysis are summarized in Table 1.	aggregate uncertainty from multiple inputs was quantified via probabilistic sensitivity analysis using uniform distributions. The range in input values was determined by 95% CIs from primary literature sources or meta- analyses. When such data were unavailable, they varied the base case value from 50% to 150%.
21) Characterizing heterogeneity	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Baseline analysis suggested that a selective, 1-time hepatitis C screening program in Canada for individuals aged 25–64 years or 45–64 years would prevent at least 9 HCV-related deaths per 10 000 persons over the lifetime of the cohort and is likely to be cost-effective, at $34 359 to $44 034 per QALY gained. The conventional upper limit of applied cost-effectiveness thresholds 50–52 varies among countries, from $50 000 to $120 000 per QALY. The results of multiple 1-way deterministic and probabilistic sensitivity analyses provided evidence that the screen-and treat approach is likely to be cost-effective, taking into consideration the uncertainty of the model's parameters.	The most important baseline characteristic of simulated patients is the degree of fibrosis according to the METAVIR scoring system. Each treatment is simulated for the duration as suggested by DGVS guidelines. After each treatment, patients can either have undetectable HCV-RNA and achieve SVR or fail therapy and be assigned to the relapser group. All-cause mortality was applied to all possible health states according to German life tables Detailed descriptions of the model's mechanics were published	The transition probabilities and SVR rates used were from observed rates of triple therapy and PR among the non-black subjects of two studies. To adjust for possible differences in SVR rates in Asian population, which has been reported with 73% prevalence of good IL28B genotype in meta-analysis, they performed a second stage analysis adjusting the SVR for Asian population based on the results of Caucasian subjects. Subset analysis showed that the BOC-based treatment regimen is cost-saving for non-cirrhotic patients who are treatment naïve and cirrhotic patients who failed the prior treatment, with 46% and 42% liver transplant reduction, respectively. For non-cirrhotic patients who failed the prior	Individual heterogeneity in chronic hepatitis C virus progression is represented by varying progression rates in sensitivity analyses.

			elsewhere.	treatment, BOC is cost-effective with 53% reduction in liver complication. Despite the initial higher cost of BOC regimens in genotype 1, model suggests that BOC regimens are still highly cost-effective compared to SOC in Asian countries, even after correcting for expected higher prevalence of favourable IL28B genotype.	
Discussion					
22) Study findings, limitations, generalizability, and current knowledge	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	A 1-time program to screen for and treat HCV infection, aimed at birth cohort populations (25–64 or 45–64 years of age), is likely to be cost-effective. The screening programs would identify people with chronic HCV infection who are asymptomatic, which would in turn allow medical treatment to be offered, if needed, according to published guidelines, ideally before development of advanced liver disease. Early recognition of infected individuals and linkage of these people with care, treatment, alcohol and other lifestyle counselling, and other forms of support could reduce the large pool of undiagnosed HCV infections, save and prolong the lives of people with such infections, and avert the lengthy hospital stays and costs associated with HCV-related end-stage liver disease, liver transplant and hepatocellular carcinoma. Limitations were discussed. Generalizable to the Canadian context	In addition to higher SVR rates, new direct-acting antivirals save long-term costs by preventing complications such as liver cirrhosis, hepatocellular carcinoma and ultimately liver transplants, thereby offsetting part of higher drug costs. Their findings are in line with the guidance published by DGVS which recommends SOF/SIM for INF ineligible or intolerant patients. In addition to higher SVR rates, the evaluated therapies save long-term costs by preventing complications such as liver cirrhosis, hepatocellular carcinoma and ultimately liver transplants, thereby offsetting part of higher drug costs.	Compared to SOC, BOC prevents more HCV liver complications from HCV genotype 1; particularly in patients who failed previous SOC. Improved SVR and shortened duration of treatment result in BOC being potentially cost saving or effective in Asian population. They concluded BOC is demonstrated to be cost-saving among treatment experienced patients compared to PR as the current standard of care, and cost-effective for treatment naïve patients, with their stated threshold. The main driving force for this result is the significant reduction of the liver complications associated with hepatitis C virus, genotype 1, particularly among patients who failed to the prior treatment. Limitations were discussed. Not generalizable to the Canadian context.	This analysis suggests that treatment with new HCV drugs is cost-effective when started with any evidence of fibrosis (F1). It assumed that patients who achieve SVR have no risk for reinfection with HCV, thus tending to overestimate cost effectiveness Market or political forces may result in significantly decreased drug costs in the next several years, and a subset of patients, given the slow progression of HCV, may be treated at a lower cost without a risk for serious clinical progression. These possibilities would make early treatment less cost-effective. Limitations were discussed. Findings on clinical outcomes appear to be generalizable to the Canadian context; however cost-effectiveness outcomes may not be very generalizable due to

			Limitations were discussed. Not generalizable to the Canadian context		differences in costs between Canada and the US.
Other					
23) Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	Funded by PAHC and one author employed by PHAC.	Funded by Janssen-Cilag GmbH Neuss, Germany.	Funded by Merck & Co., Inc. and supported by staff and personnel from Merck & Co., Inc., and MSD Pharma (Singapore) Pte. Ltd.	Funded by Blue Shield of California Foundation and the California Health Care Foundation (through the Institute for Clinical and Economic Review); by the Clinical and Translational Sciences Institute, University of California, San Francisco; and by grant DA15612 from the National Institute on Drug Abuse, National Institutes of Health.
24) Conflicts of interest	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	No conflicts per CMAJ/ ICMJE.	Conflicts reported: The study was funded by a pharmaceutical company. One author was on the advisory committee and received honorarium and/or research funding from multiple sponsors. The study was supported by staff and personnel from two sponsors. Published in BMC Infectious Diseases.	Disclosure statement: The manuscript is supported by staff and personnel from two pharmaceutical companies. The main author has been on the advisory committee and has received honorarium and/or research funding from 6 sponsors. All other authors declare no competing interests. Published in International Medical Press	Conflict of Interest Disclosures: None reported. Published in JAMA.

Summary of Evaluation of Modelling Studies

Four modelling studies[6,38-40] met the PICO criteria for inclusion in this review. However, once the critical appraisals (Drummond Checklist[22] and CHEERS[23]) were conducted on each of the modelling studies, baseline assumptions and risks compared between models, and upon consensus by the Working Group, it was decided that the Chahal 2016[38] model was the most appropriate model to use for this review. This model also provided evidence for the greatest number of patient important outcomes by fibrosis score compared to the others.

The following are some specific concerns regarding the models:

Dan 2015[39]
Although industry funding alone, is not necessarily a sign of bias, the principal investigator received funding/honorarium from pharmaceutical companies. Additionally, the model's effectiveness estimates were based on a single RCT (SPRINT-2) and the report gave no rationale as to why that study was selected. Finally, the treatment regimens were modified to meet treatment guidelines in Singapore and the paper did not provide details on the choice of model used, its assumptions, uncertainty, or the analytic methods used.

Gissel 2015[40]
The Gissel 2015 model was also industry funded and the effectiveness estimates were only partially provided. Two of the four treatment regimens, PR and Boceprevir+PR, did not have parameter sources (clinical trials) associated with them. The paper did not describe the population characteristics, or the assumptions, uncertainty, or the analytic methods used.

Wong 2015[6]
The Wong 2015 model was not industry funded. It used HCV RNA accuracy for the confirmatory test related to screening and did not adjust SVR rates by fibrosis stage, only by genotype and response to treatment (naïve, relapser, etc.). Also, the baseline fibrosis scores used in the Wong model would be expected to lead to more optimistic results, especially in the later fibrosis stages (Ages 55-64: F0=0%; F1=15%; F2=15%; F3=34%; F4=36%) than were used in the Chahal[38] model (Age 60: F0=17%; F1=35%; F2=22%; F3=14%; F4=12%). The Wong model also included telaprevir which is no longer in use in Canada and included fewer treatment regimens as compared with the Chahal study[38].

Chahal 2016[38]

The Chahal 2016 modelling study assessed the cost-effectiveness of treating HCV genotype 1 treatment-naïve patients by stage of liver fibrosis in the United States population. The study used a decision-analytic model with disease states that reflected progression through the five Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis stages (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis). Patients were followed to the development of select outcomes, namely decompensated cirrhosis, hepatocellular carcinoma, liver transplants and death from liver complications. Regression of liver damage after successful antiviral therapy was also accounted for in the model. In addition to no therapy, six HCV treatment regimens were considered: PR, sofosbuvir + PR, sofosbuvir + ribavirin (RBV), sofosbuvir + simeprevir, sofosbuvir + ledipasvir, and ombitasvir/paritaprevir/ritonavir+dasabuvir ± RBV.

The goal of treatment was to achieve a sustained virological response (SVR) 12 weeks after treatment completion.

The study was funded by the Blue Shield of California Foundation and the California Health Care Foundation (through the Institute for Clinical and Economic Review); by the Clinical and Translational Sciences Institute, University of California, San Francisco; and by grant DA15612 from the National Institute on Drug Abuse, National Institutes of Health. The Institute for Clinical and Economic Review collaborated on the design, conduct, and reporting of this study. The other funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor decision to submit the manuscript for publication.

As noted, the modelling study was based on many assumptions and the input parameters were not always obtained through a systematic review of the evidence. For instance, the model was validated against the results of empirical natural history studies and prior models, and the authors used the results of meta-analyses as input for some of their key parameters such as the natural history of the disease and SVR rates. However, the data linkages between SVR rates and long-term outcomes (e.g. hepatic mortality) were based on single studies that were not selected through the conduct of a systematic review of the evidence.

Additionally, the model simulates 1,000 individuals to represent a single 60 year old (in 2015) modelled individual all the way through to long term outcomes. Because progression parameters are based on age, a more realistic approach would have been to randomly simulate blocks of modelled individuals (e.g. 50-54, 55 to 59, etc.) 1,000 times to allow for the different progression parameters to play out. The model was sensitive to all of these assumptions and it is not clear that all of these assumptions are valid.

Rates of SVR and treatment discontinuation were obtained from meta-analyses of phase 2 and 3 clinical trials. The probabilities of transitioning from one state to the next were based on a review of published literature. The initial model cohort followed the distribution in fibrosis stage observed with HCV infection in the US population. Patient characteristics were based on data from a 2010 national U.S. health survey.

Appendix B

1-Search Strategy (up until February 2015)

Source: CADTH Therapeutic Review on Drugs for Chronic Hepatitis C Infection: Clinical Review July 2015[9]

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 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.
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,oemezd
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 (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)

2-Search Strategy (February 2015 to November 2015)

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

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

#	Searches	Results
1	(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.	2644
2	*telaprevir/	1333
3	(boceprevir* or bocepravir* 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

[a] The original search strategies created by CADTH[9] were not replicated exactly. Subsequent search updates were conducted in the Cochrane Database of Systematic Reviews instead of Cochrane CENTRAL Register of Controlled Trials, and Ovid Medline and Embase searches applied an additional human limit. As such, there is a chance that some articles that would have otherwise been retrieved were not identified.

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 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.	1306
2	(402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm.	740
3	(boceprevir* or bocepravir* 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	646

	PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab,ot,sh,hw,rn,nm.	
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 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) all text	236
2	(boceprevir* or bocepravir* 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 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 | Completed | Studies With Results | updated from 02/04/2015 to 11/30/2015	5
2	boceprevir* OR bocepravir* 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 11/30/2015	5
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	15

	| Completed | Studies With Results | updated from 02/04/2015 to 11/30/2015	
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:	 First search: November 20, 2015 Second search: August 10, 2016
Keywords:	Hepatitis C, telaprevir, boceprevir, simeprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816 and ABT-530
Limits:	First search: From February 2015 to November 2015, English only Second search: From February 2015 to August 2016, 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 C

Ottawa Evidence Review Synthesis Centre
Treatment for Hepatitis C Virus
Pre-publication updated search – DRAFT brief report
23 January 2017

Methods

MEDLINE, EMBASE, and Cochrane Central search strategies (as provided by the Public Health Agency of Canada [PHAC]) were executed on November 21, 2016 to update the November 18, 2015 search (Appendix B-1; see Note 1 below). From the literature yield, duplicates were removed.

The selection criteria (PICOS) from the original review (as provided by PHAC) were used, but only randomized controlled trials (RCTs) for both benefits and harms key questions were included. We did not include modelling studies in this update. Title and abstracts were screened independently by 2 reviewers (James Galipeau, Kelly Cobey) and disagreements were resolved by consensus. Full-text screening was done independently by two of three reviewers (James Galipeau, Kelly Cobey, Doreen Whelan), and disagreements were resolved by consensus.

No methodological assessment was performed.

Literature search results

Of 966 records identified from the updated search strategy (163 obtained from the grey literature search), 924 records remained after the removal of duplicates for assessment. During title and abstract screening, 628 records were excluded (Appendix C-1). Of the 296 full-text articles that were assessed, 295 records were removed (Appendix E and Figure 1) and one article (Wei, 2016. *J Gastroenterology and Hepatology*. 31, 912-920) met the inclusion criteria. However, it was included in the previous PHAC report, despite it being outside of the date range of that PHAC report search strategy.

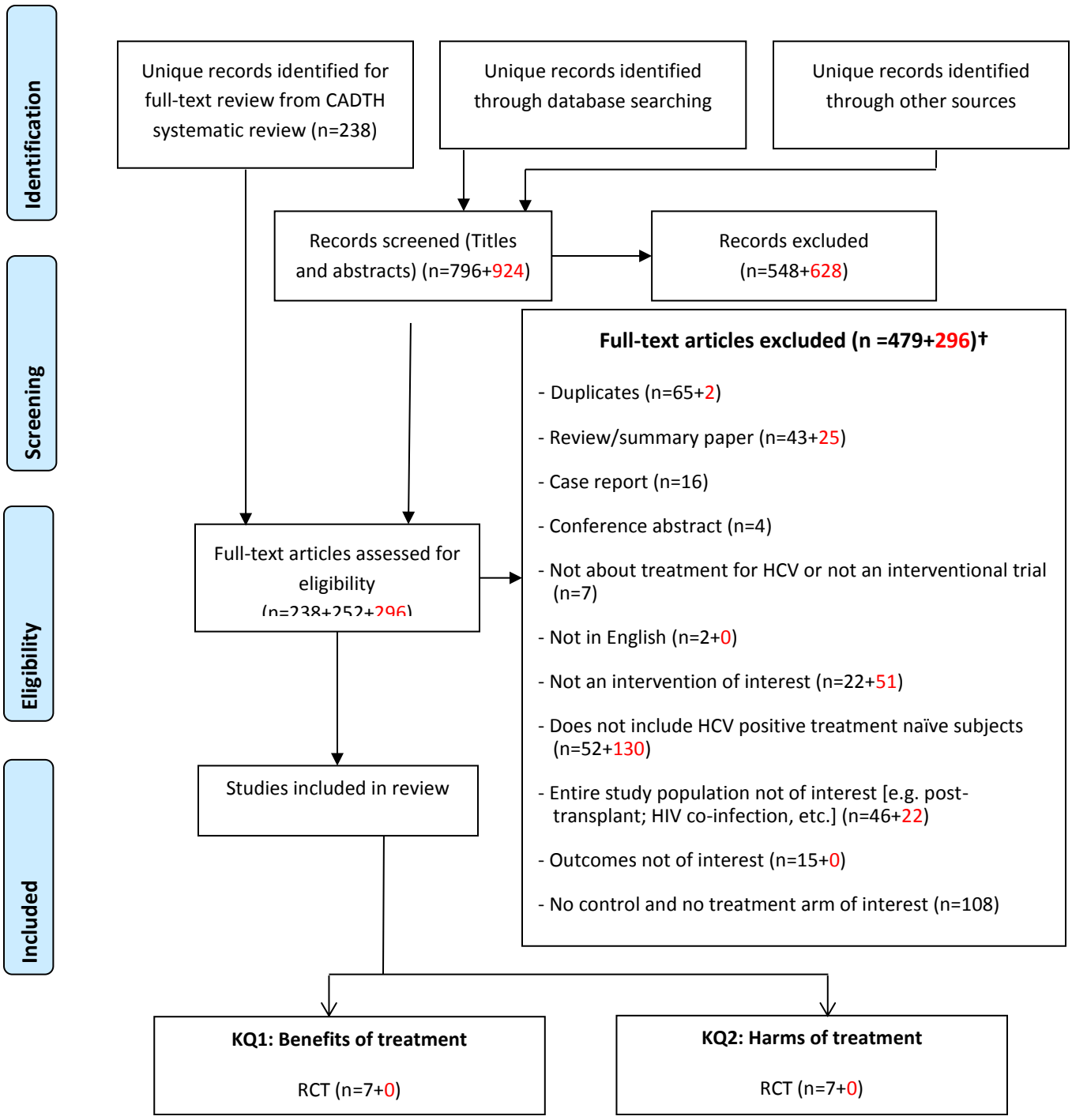
In addition, two Errata were discovered relating to two previously included studies (Jacobson, 2014; Manns, 2014). Here are the verbatim notices published in The Lancet (Volume 387; Issue 10030; page 1816):

« 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—In this Article, an error in the scoring algorithm caused an error in the data for the Center for Epidemiologic Studies Depression

Figure 1. PRISMA Flow Diagram[19]

*Includes numbers from previous update (in black) and current update (in red).



†The list of reasons for exclusion of full-text articles is not identical between reports. Items for which the reasons for exclusion are the same between reports identify the number of studies excluded for both the previous report (in black) and the current report (in red). Items where n=0 indicate that the reason for exclusion was included but no instances were found.

Scale (CES-D) score. Supplementary figure 4 has been replaced and the means updated. A new appendix has been uploaded as of April 28, 2016. »

« 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—In this Article, an error in the scoring algorithm caused an error in the data for the Center for Epidemiologic Studies Depression Scale (CES-D) score. In the second sentence of the 14th paragraph of the Results, the statistical difference in the CES-D area under the curve at 60 weeks between treatment groups has been amended from not significant (p=0·079) to significant (p=0·040). Supplementary figure 4 has been replaced and a new appendix uploaded. These changes have been made as of April 28, 2016. »

APPENDIX C-1- SEARCH STRATEGIES

Hepatitis C Treatment

Final Strategies

2016 November 18

(Note: Based on original searches)

Hep C Treatment – DRUGS

2016 Nov 18

OVID Multifile

Database: Embase <1974 to 2016 November 18>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 (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. (6471)
2 (402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm. (4060)
3 (boceprevir* or bocepravir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab,ot,sh,hw,rn,nm. (4613)
4 (394730-60-0 or 89BT58KELH).rn,nm. (2971)
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. (5260)
6 (1190307-88-0 or WJ6CA3ZU8B).rn,nm. (2560)
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. (2797)
8 (923604-59-5 or 9WS5RD66HZ).rn,nm. (1506)
9 (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab,ot,sh,hw,rn,nm. (2227)
10 (1256388-51-8 or 013TE6E4WV).rn,nm. (756)
11 (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab,ot,sh,hw,rn,nm. (1425)
12 (1216941-48-8 or OU2YM37K86).rn,nm. (374)
13 (ombitasvir* or ABT 267 or ABT267).ti,ab,ot,sh,hw,rn,nm. (1302)
14 (1258226-87-7 or 2302768XJ8).rn,nm. (408)
15 (dasabuvir* or ABT 333 or ABT333).ti,ab,ot,sh,hw,rn,nm. (1254)
16 (1132935-63-7 or DE54EQW8T1).rn,nm. (441)
17 (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab,ot,sh,hw,rn,nm. (2545)
18 (1009119-64-5 or LI2427F9CI).rn,nm. (1224)
19 (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab,ot,sh,hw,rn,nm. (1097)
20 (630420-16-5 or S9X0KRJ00S).rn,nm. (572)
21 (grazoprevir* or MK 5172 or MK5172).ti,ab,ot,sh,hw,rn,nm. (597)

22 (1350462-55-3 or 1350514-68-9 or 4O2AB118LA or 8YE81R1X1J).rn,nm. (183)
23 (elbasvir* or MK 8742 or MK8742).ti,ab,ot,sh,hw,rn,nm. (417)
24 (1370468-36-2 or 632L571YDK).rn,nm. (135)
25 (beclabuvir* or BMS 791325 or BMS791325).ti,ab,ot,sh,hw,rn,nm. (264)
26 (958002-33-0 or MYW1X5CO9S).rn,nm. (108)
27 (GS5816 or GS 5816).ti,ab,ot,sh,hw,rn,nm. (59)
28 (ABT-530 or ABT530).ti,ab,ot,sh,hw,rn,nm. (59)
29 (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab,ot,sh,hw,rn,nm. (145)
30 or/1-29 (13717)
31 30 not (conference abstract or Journal: conference abstract).pt. (9524)
32 limit 31 to (english language and humans) (7531)
33 (2015$ or 2016$).dc,ed. (6888485)
34 32 and 33 (3667)
35 ("20151113" or "20151114" or "20151115" or "20151116" or "20151117" or "20151118" or "20151119" or 2015112* or 201512* or 2016*).dc. (3213568)
36 34 and 35 (1385)
37 36 use ppez (185)
38 (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. (4298)
39 *telaprevir/ (1703)
40 (boceprevir* or bocepravir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab. (2966)
41 *boceprevir/ (1104)
42 (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. (3788)
43 *sofosbuvir/ (1678)
44 (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab. (1825)
45 *simeprevir/ (680)
46 (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab. (1446)
47 *ledipasvir/ (262)
48 (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab. (809)
49 *paritaprevir/ or *veruprevir/ (119)
50 (ombitasvir* or ABT 267 or ABT267).ti,ab. (776)
51 *ombitasvir/ (128)
52 (dasabuvir* or ABT 333 or ABT333).ti,ab. (707)
53 *dasabuvir/ (239)
54 (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab. (1680)
55 *daclatasvir/ (649)
56 (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab. (670)
57 *asunaprevir/ (313)
58 (grazoprevir* or MK 5172 or MK5172).ti,ab. (314)
59 *grazoprevir/ (68)
60 (elbasvir* or MK 8742 or MK8742).ti,ab. (246)
61 *elbasvir/ (68)
62 (beclabuvir* or BMS 791325 or BMS791325).ti,ab. (121)
63 *beclabuvir/ (36)
64 (GS5816 or GS 5816).ti,ab. (34)

65 (ABT-530 or ABT530).ti,ab. (51)
66 (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab. (142)
67 or/38-66 (10845)
68 67 not conference abstract.pt. (6654)
69 limit 68 to (human and english language) (4938)
70 (2015* or 2016*).dd,em. (30800159)
71 69 and 70 (3999)
72 ("20151113" or "20151114" or "20151115" or "20151116" or "20151117" or "20151118" or "20151119" or 2015112* or 201512* or 2016*).dc,dd. (3227607)
73 71 and 72 (961)
74 73 use oemezd (786)
75 37 or 74 (971)
76 remove duplicates from 75 (799) [TOTAL UNIQUE RECORDS]
77 76 use ppez (172) [MEDLINE UNIQUE RECORDS]
78 76 use oemezd (627) [EMBASE UNIQUE RECORDS]

****
Cochrane Library

Search Name: Hep C Treatment - Health Canada
Date Run: 22/11/16 16:55:48.487
Description: CTFPHC (OHRI) - 2016 Nov 21 Update

ID Search Hits
#1 (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) 276
#2 (boceprevir* or bocepravir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520) 203
#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) 242
#4 (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad) 110
#5 (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796) (Word variations have been searched) (Word variations have been searched) 1
#6 (paritaprevir* or veruprevir* or ABT 450* or ABT450*) (Word variations have been searched) 105
#7 (ombitasvir* or ABT 267 or ABT267) (Word variations have been searched) 93
#8 (dasabuvir* or ABT 333 or ABT333) (Word variations have been searched) 86
#9 (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza) 99
#10 (asunaprevir* or Sunvepra or BMS 650032 or BMS650032) 53
#11 (grazoprevir* or MK 5172 or MK5172) (Word variations have been searched) 40
#12 (elbasvir* or MK 8742 or MK8742) (Word variations have been searched) 31
#13 (beclabuvir* or BMS 791325 or BMS791325) 21
#14 (GS5816 or GS 5816) 13
#15 (Viekira or Viekirax or Exviera or Holkira or Harvoni) 5
#16 {or #1-#15} 896
#17 [mh Animals] 7777
#18 [mh "Animal Experimentation"] 4

#19	[mh "Models, Animal"]	404
#20	[mh Vertebrates]	6240
#21	{or #17-#20}	7831
#22	#16 not #21 Online Publication Date from Nov 2015 to Nov 2016	4

DSR - 4

Appendix D
List of Included Studies and Study Characteristics

Study, Design, Objective, Methods, Duration, Funding	Participants	Intervention	Outcomes
Fried 2013[28] The Randomized PILLAR Study **Scott 2014**[33] **Quality of Life Study** Double-blind RCT, Response-guided therapy, Phase 2 The phase IIb, double-blind, placebo-controlled PILLAR trial investigated the efficacy and safety of two different simeprevir doses administered once-daily (QD) with pegylated interferon (Peg-IFN)-α-2a and ribavirin (RBV) in treatment-naive patients with HCV genotype 1 infection. Enrollment began in May 2009, and the study was completed in April 2011. Funded by Janssen Research & Development, LLC	Recruitment: Adult patients with CHC were eligible for participation if they had plasma HCV RNA >100,000 IU/mL, were infected with HCV genotype 1, had never received (Peg)IFN, RBV, or other approved or investigational agents for chronic HCV infection, and were deemed eligible to be treated with Peg-IFN-based regimens according to standard criteria were recruited from clinical settings in US, Australia, Austria, Belgium, Canada, Denmark, France, Germany, New Zealand, Norway, Poland, Russian Federation, Spain Exclusion Criteria: Patients were excluded if they had cirrhosis on liver biopsy (required within 24 months of enrollment), coinfection with human immunodeficiency virus or hepatitis B, platelet count <90,000/mm3, or hemoglobin <12 g/dL for females and 13 g/dL for males. Genotype: 1, 1a, 1b; Age: 18-69(46.5); 55.2% male Number of Arms: 5; Total Participants: 386 Range of Fibrosis/Cirrhosis at Baseline: F0=9-16%; F1=33-46%; F2=32-35%, F3=9-23% Excluded patients with cirrhosis	Control: PBO +PEG 180µg weekly + RBV (1000-1200mg by weight) daily for 48 weeks - 77 participants Arm 1: SIM 75mg daily + PEG 180µg weekly + RBV (1000-1200mg by weight) daily for 12 weeks followed by PBO + PEG 180µg weekly + RBV (1000-1200mg by weight) daily for 12 weeks followed by PR for 0-24weeks (RGT) - 78 participants Arm 2: SIM 75mg daily + PEG 180µg weekly + RBV (1000-1200 mg by weight) daily for 24 weeks, followed by PR for 0-24weeks (RGT) - 75 participants Arm 3: SIM 150mg daily + PEG 180µg weekly + RBV (1000-1200 mg by weight) daily for 12 weeks followed by PBO daily + PEG 180 µg weekly + RBV (1000-1200 mg by weight) daily for 12 weeks followed by PR for 0-24weeks (RGT) - 77 participants Arm 4: SIM 150 mg daily + PEG 180µg weekly + RBV (1000-1200 mg by weight) daily for 24 weeks, followed by PR for 0-24weeks (RGT) - 79 participants 72 weeks follow-up	SVR12, SVR24, SVR72, mortality (all-cause), anemia, flu-like symptoms, neutropenia, psychological adverse events, rash, withdrawals due to adverse events, quality of life
Hayashi 2014[29], CONCERTO-1 trial Double-blind RCT, Response-	Recruitment: Treatment-naïve male and female patients aged 20–70 years with documented chronic genotype 1 HCV infection and plasma HCV RNA P5.0 log10 IU/ml at	Control: PBO + PEG 180µg once weekly + RBV (600-1000mg by weight) daily for 12weeks, followed by PR for 24-48 weeks (RGT) – 60 participants	SVR12, SVR24, mortality (all-cause), anemia, neutropenia,

guided therapy, Phase 3 To further explore efficacy and safety of simeprevir combined with PegIFN/RBV in treatment-naive patients with HCV genotype 1 infection in Japan. The study was conducted from January 17, 2011 to October 22, 2012. Funded by Janssen Pharmaceutical K.K.	screening were eligible and recruited from 37 sites in Japan. Exclusion Criteria: Key exclusion criteria included liver cirrhosis, hepatic failure, any other liver disease of non-HCV etiology and co-infection with HIV-1, HIV-2, hepatitis B, or non-genotype 1 HCV. Genotype 1; Age: 23-69 (55); 34.4% male Number of Arms: 2; Total Participants: 183 Range Fibrosis/Cirrhosis at Baseline: F0=0-7%; F1=68-75%; F2=20-21%; F3=4-5% Excluded patients with cirrhosis	Arm 1: SIM 100mg daily + PEG 180µg weekly + RBV (600-1000mg by weight) daily for 12 weeks + PR for 24-48 weeks (RGT) - 123 participants 72 weeks follow-up	psychological adverse events, rash, withdrawals due to adverse events
Jacobson 2014[30], QUEST-1 Double-blind RCT, Response-guided therapy, Phase 3 The purpose of this study is to investigate the effectiveness and safety of Simeprevir compared with placebo in participants who are infected with genotype 1 hepatitis C virus who have never received treatment before. Participants will also receive peginterferon alpha-2a and ribavirin as part of their treatment. The study was conducted from January 18, 2011 to January 29, 2013.	Recruitment: Eligible patients were aged 18 years and older with confirmed chronic HCV genotype 1 infection, screening plasma HCV RNA concentration greater than 10 000 IU/mL, and no history of treatment for HCV Eligible patients were aged 18 years and older with confirmed chronic HCV genotype 1 infection, screening plasma HCV RNA concentration greater than 10 000 IU/mL, and no history of treatment for HCV. Multi-centre trial in 13 countries: Australia, Canada, Germany, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russia, Spain, Ukraine, the UK, and the US Exclusion Criteria: Exclusion criteria included hepatic decompensation or any non-HCV-related liver disease; co-infection with HIV, hepatitis B virus, or non-genotype 1 HCV infection; significant laboratory abnormalities; any other active disease; and male or female patients who had, or were planning to	Control: PBO + PEG 180 µg/week + RBV (1000-1200 mg by weight) daily for 12 Weeks followed by PR until week 48 - 130 participants Arm 1: SIM 150 mg once daily + PEG 180 µg/week + RBV (1000 -1200 mg by weight) daily for 12 weeks, followed by PR until Week 24. Treatment stopped at Week 24 for participants who achieved HCV RNA < 25 IU/mL detectable or undetectable at Week 4 and undetectable HCV RNA at Week 12. Other participants continued PR until Week 48. (RGT) - 264 participants 72 weeks follow-up	SVR12, SVR24, SVR72, Mortality (all-cause), Anemia, Flu-like symptoms, Neutropenia, Psychological adverse events, Rash, Withdrawals due to Adverse Events

Funded by Janssen Infectious Diseases–Diagnostics	conceive. Genotype 1, 1a, 1b; Age 19 to 68 (48), 56.3% male 2 Arms; 394 Participants Range Fibrosis/Cirrhosis at Baseline: F0-F1= 38-45%; F2=25-31%; F3=17-18%; F4= 12-13%		
Lawitz 2013-1[36], FISSION trial **Younossi 2014[35] Quality of Life Study** Double-blind RCT, Non-inferiority study, Open-label, Phase 3 Conducted two phase 3 studies to evaluate the efficacy and safety of 12 weeks of therapy with regimens containing SOF in patients who had not previously received treatment for HCV infection. The study was conducted from December 2011 through May 2012 Funded by Gilead Sciences	Recruitment: Male or female aged 18 years, confirmation of HCV infection, HCV RNA 104 IU/ml at Screening, approximately 20% of patients could have evidence of cirrhosis, HCV treatment naïve. Body mass index (BMI) 18 kg/m2, screening electrocardiogram (ECG) without clinically significant abnormalities,. Setting unconfirmed, but some authors from liver clinics/centres in US, Australia, New Zealand, Italy, Sweden, and the Netherlands. Exclusion Criteria: Key exclusion criteria included prior treatment for HCV with INF, RBV or DAAs targeting the HCV NS5B polymerase, hepatocellular carcinoma, treatment with any investigational drug or device within 30 days of screening visit, pregnant or nursing female, or male with pregnant female partner, chronic non-HCV liver disease, HIV or Hep B infection. psychiatric illness, pulmonary or cardiac disease. Genotype 1; Age 19-77 (48); 65.5% male 2 Arms, 499 Participants	Control: PBO + PEG 180 µg once weekly +RBV (1000-1200mg by weight) daily for 24 weeks - 243 participants Arm 1: SOF 400 mg orally once daily + RBV (1000 -1200 mg by weight)daily for 12 weeks - 256 participants 36 weeks follow-up	SVR12, SVR24, mortality (all-cause), anemia, flu-like symptoms, neutropenia, psychological adverse events, rash, withdrawals due to adverse events, quality of life

	Range Fibrosis/Cirrhosis at Baseline: Control - 50 participants with cirrhosis (21%) Arm 1 - 50 participants with cirrhosis (20%)		
Lawitz 2013-2[37], NCT01188772 trial Double-blind RCT, Phase 2 To assess the safety and efficacy of sofosbuvir in treatment-naive patients with genotype 1–3 HCV infection The study was conducted from August 16, 2010 through May 11, 2012. Funded by Gilead Sciences	Recruitment: Male or female adults 18–70 years, treatment-naive with HCV genotypes 1–3 and an HCV RNA concentration of 50 000 IU/mL or greater, from 22 clinical centres in the US. Exclusion Criteria: Key exclusion criteria included cirrhosis, hepatitis B virus or HIV, psychiatric illness, pulmonary or cardiac disease, seizure disorder, or other serious comorbid disorders were excluded. Genotype 1, 2, 3; Age 18-70 (50); 60% male 3 Arms, 121 Participants Range Fibrosis/Cirrhosis at Baseline: No or minimal 12-25%; portal fibrosis 73-81%; bridging fibrosis 2-8% Excluded patients with cirrhosis	Control: SOF 200mg + PEG 180µg weekly + RBV)1000-1200mg by weight daily) for 12weeks, plus PR x12-36 depending on viral response - 26 participants Arm 1: SOF 200mg + PEG 180µg weekly + RBV)1000-1200mg by weight daily) for 12weeks, plus PR x12-36 depending on viral response - 48 participants Arm 2: SOF 400mg + PEG 180µg weekly + RBV (1000-1200mg by weight) daily for 12 weeks + PR for 12 to 36 depending on viral response - 47 participants 24 or 48 weeks follow-up depending on viral response	SVR12, SVR24, Anemia, Flu-like symptoms, Neutropenia, Psychological adverse events, Rash, Withdrawals due to Adverse Events
Manns 2014[31], QUEST-2 trial Double-blind RCT, Response-guided therapy, Phase 3 The study investigated the efficacy, safety, and tolerability of simeprevir versus placebo in combination with peginterferon alfa 2a plus ribavirin or peginterferon alfa 2b plus ribavirin in treatment-naive patients who had chronic HCV genotype 1 infection in the	Recruitment: Men and women aged 18 years and older with confirmed chronic HCV genotype 1 infection, plasma HCV RNA concentration at screening of greater than 10 000 IU/mL, and no history of treatment of HCV infection with an approved or an investigational drug. Patients with cirrhosis were eligible if an ultrasound assessment within the 6 months before the study did not show any signs of hepatocellular carcinoma. Setting assumed specialized clinics since those who were recruited had liver biopsy and possible liver ultrasound: Austria, Belgium, Bulgaria, Germany, France, Poland,	Control: PBO 150 mg once daily 12 weeks + PEG 180 µg + RBV (1000–1200 mg/day or 800–1400 mg/day by weight) for 48 weeks - 134 participants Arm 1: SIM 150 mg daily for 12 weeks + PEG or PR for 24 or 48 weeks - 257 participants 72 weeks follow-up	SVR12, SVR24, SVR 72, mortality (all-cause), anemia, flu-like symptoms, neutropenia, psychological adverse events, rash, withdrawals due to adverse events

phase 3 QUEST-2 trial. The study was conducted from January 18, 2011 and February 5, 2013 Funded by Janssen Infectious Diseases–Diagnostics.	Portugal, Slovakia, Spain, and The Netherlands. Randomisation to PegIFNα-2b did not take place in Turkey, the United States, Argentina and Brazil. Exclusion Criteria: Key exclusion criteria included hepatic decompensation, any non-HCV-related liver disease, or co-infection with HIV, hepatitis B virus, or non-genotype 1 HCV Genotype 1, 1a, 1b; Age 18-73(46), 55.5% male 2 Arms, 391 Participants Range Fibrosis/Cirrhosis at Baseline: F0-F1=45-52%; F2=26-31%; F3=13-15); F4=7-11%		
NCT01725529 2015[32], TIGER Trial **Wei 2016[34] Quality of Life Study** Double-blind RCT, Response-guided therapy, Phase 3 Investigate the efficacy, pharmacokinetics, safety and tolerability of tmc435 vs. placebo as part of a treatment regimen including peginterferon alfa-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects.	Recruitment: Men and women aged 18-70 years with HCV infection (presence of contraindications for a liver biopsy in patients who are otherwise deemed eligible for participation does not exclude the patient from participation), genotype 1 and plasma HCV RNA of > 10,000 IU/mL at screening. Conducted at sites in China and Republic of Korea. Exclusion Criteria: Key exclusion criteria included prior treatment with any approved or investigational drug for the treatment of HCV, co-infection with hepatitis B virus or HIV. Genotype 1; Age 18-68(45); 51.6% male 3 Arms, 457 Participants Range Fibrosis/Cirrhosis at Baseline:	Control: PBO + SIM 150 mg for 12 weeks once daily + RBV(1000-1200mg by weight) daily + PEG 180µg weekly for 48 weeks - 152 participants Arm 1: SIM 100 mg once daily for 12 weeks + PEG , RBV + PBO matching to SIM 150 mg, followed by PegIFNα-2a and RBV alone for 24 t0 48 weeks (RGT) - 153 participants Arm 2: SIM 150 mg once daily for 12 weeks + PEG , RBV+ PBO matching to SIM 100 mg, followed by PegIFNα-2a and RBV alone for 24 t0 48 weeks (RGT) - 152 participants 120 weeks follow-up	SVR12, SVR24, SVR 72, anemia, flu-like symptoms, neutropenia, psychological adverse events, rash, withdrawals due to adverse events, quality of life

The study was conducted from November 2012 and November 2014 Funded by Janssen R&D Ireland	Not provided		
Chahal 2016[38] Modelling Study The objective of this study was to determine the most cost-effective liver fibrosis stage at which to initiate treatment with direct-acting antiviral agents in US treatment-naive patients with HCV genotype 1 infection and was based on commonly accepted thresholds. Data were collected from March 1 to September 1, 2014, and analyzed from September 1, 2014, to June 30, 2015 Funded by the Blue Shield of California Foundation and the California Health Care Foundation (through the Institute for Clinical and Economic Review); by the Clinical and Translational Sciences Institute, University of California, San Francisco; and by grant DA15612 from the National Institute on Drug Abuse, National Institutes of Health	Model parameters: In the base-case scenario, they portray a cohort of 60-year-old patients (birth year,1955) weighing 75 kg who are already aware of their HCV infection but are treatment-naïve. Rationale: The characteristics of patients in the analytic cohort were specified based on data from the 2010 National Health And Nutrition Examination Survey, indicating that 70% of HCV infected persons were born from 1945 to 1965. As this cohort ages, the incidence of complicated liver conditions will increase. Other age cohorts ranging from 20 to 70 years are used for scenario analyses. The model does not distinguish patients on the basis of viral concentration, sex, or race, although these factors may affect treatment outcomes. The model considered only patients mono-infected with HCV, excluding co-infections with hepatitis B virus and HIV They adopted a societal perspective, including all direct medical costs for HCV management and therapy. The Markov model health states, progression and regression transition probabilities and proportions are derived from published literature. The Markov model cycles (either quarterly, half-year or full year) correspond to the duration of the therapy being analyzed. For each cycle, the patients will accrue the corresponding costs and QALYs	Arm 1: No Treatment Arm 2: PR48 Arm 3 SOF + PR 12 Arm 4 SOF+RVB24 Arm 5 SOF+ SIM 12/24; Arm 6 SOF+LDV 8/12 Arm 7 SOF=LDV 12 Arm 8 Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (3D) ±Ribavirin 12/24 * Treat All vs. treat at F3/F4with each of the seven therapy options * Treatment by Fibrosis Stage with each of the seven therapy options Policy Description of policy: 1)Treat all – Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4) 2)Treat at F1 – Wait and treat only when patients reach stages F1, F2, F3 and F4 3)Treat at F2 – Wait and treat only when patients reach stages F2, F3 and F4 4)Treat at F3 – Wait and treat only when patients reach stages F3 and F4 5)Treat at F4 – Wait and treat only when patients reach stage F4 6)No Treatment – the cohort cycles through the model without treatment The objective of this study was to determine the most cost-effective liver fibrosis stage at which to initiate treatment with direct-acting antiviral agents in US treatment-naive patients	Mortality (hepatic), hepatocellular carcinoma, hepatic decompensation, need for liver transplantation The model also produces discounted lifetime QALYs and direct medical costs for each strategy. It then calculates incremental cost-effectiveness ratios (ICERs) as the ratio of the difference in costs between treatment strategies divided by the difference in QALYs.

	of the health state over a lifetime. Genotype 1; a cohort of 60-year-old patients Range Fibrosis/Cirrhosis at Baseline (input parameter): F0=17%; F1=35%; F2=22%; F3=14%; F4=12% Assumptions: - assumed that patients who achieve SVR have no risk for reinfection with HCV, thus tending to overestimate cost effectiveness - the model does not consider benefits for patients who receive therapy but do not achieve SVR - the model does not consider the reduction in HCV transmission to seronegative individuals as a consequence of successful therapy - the model did not consider extended treatment for patients with slow responses or the repeated treatment of patients who do not achieve SVR - the model uses aggregated annualized transition probabilities to simulate progression from one clinical state to the next, adjusted for age but not for other individual traits. This approach focuses the overall simulation on population-level natural history. Individual heterogeneity in chronic hepatitis C virus progression is represented by varying progression rates in sensitivity analyses - the analysis took into account only direct medical costs, omitting potential gains in productivity -the model did not simulate changing drug costs over time and how that would affect the	with HCV genotype 1 infection and was based on commonly accepted thresholds. We present an analysis of a fixed-dose combination of sofosbuvir and ledipasvir (hereinafter, sofosbuvir-ledipasvir). Other regimens are analyzed in eTable 1 in the Supplement. Lifetime	

	cost-effectiveness of early treatment. Market or political forces may result in significantly decreased drug costs in the next several years, and a subset of patients, given the slow progression of HCV, may be treated at a lower cost without a risk for serious clinical progression. These possibilities would make early treatment less cost-effective.		

Appendix E – Excluded Studies

Excluded Studies from Electronic Search conducted on November 18, 2015

#	Article	Exclusion Criteria
1.	M. Bourlière,J. -P Bronowicki,V. de Ledinghen,C. Hézode,F. Zoulim,P. Mathurin,A. Tran,D. G. Larrey,V. Ratziu,L. Alric,R. H. Hyland,D. Jiang,B. Doehle,P. S. Pang,W. T. Symonds,G. M. Subramanian,J. G. McHutchison,P. Marcellin,F. Habersetzer,D. Guyader,J. -D Grangé,V. Loustaud-Ratti,L. Serfaty,S. Metivier,V. Leroy,A. Abergel,S. Pol. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: A randomised, double-blind, phase 2 trial (SIRIUS). *The Lancet Infectious Diseases.* 2015. 15:397	Population
2.	P. Andreone,M. G. Colombo,J. V. Enejosa,I. Koksal,P. Ferenci,A. Maieron,B. Müllhaupt,Y. Horsmans,O. Weiland,H. W. Reesink,L. Rodrigues Jr.,Y. B. Hu,T. Podsadecki,B. Bernstein. 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	Population
3.	N. Afdhal,K. R. Reddy,D. R. Nelson,E. Lawitz,S. C. Gordon,E. Schiff,R. Nahass,R. Ghalib,N. Gitlin,R. Herring,J. Lalezari,Z. H. Younes,P. J. Pockros,A. M. Di Bisceglie,S. Arora,G. M. Subramanian,Y. Zhu,H. Dvory-Sobol,J. C. Yang,P. S. Pang,W. T. Symonds,J. G. McHutchison,A. J. Muir,M. Sulkowski,P. Kwo. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *New England Journal of Medicine.* 2014. 370:1483	Population
4.	M. Charlton,E. Gane,M. P. Manns,R. S. Brown,M. P. Curry,P. Y. Kwo,R. J. Fontana,R. Gilroy,L. Teperman,A. J. Muir,J. G. McHutchison,W. T. Symonds,D. Brainard,B. Kirby,H. Dvory-Sobol,J. Denning,S. Arterburn,D. Samuel,X. Forns,N. A. Terrault. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology.* 2015. 148:108	Population
5.	D. Dieterich,J. K. Rockstroh,C. Orkin,F. Gutierrez,M. B. Klein,J. Reynes,U. Shukla,A. Jenkins,O. Lenz,S. Ouwerkerk-Mahadevan,M. Peeters,G. De La Rosa,L. Tambuyzer,W. Jessner. Simeprevir (TMC435) with pegylated interferon/ribavirin in patients coinfected with HCV genotype 1 and HIV-1: a phase 3 study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2014. 59:1579	Population
6.	M. P. Curry,X. Forns,R. T. Chung,N. A. Terrault,R. Brown,J. M. Fenkel,F. Gordon,J. O'Leary,A. Kuo,T. Schiano,G. Everson,E. Schiff,A. Befeler,E. Gane,S. Saab,J. G. McHutchison,G. M. Subramanian,W. T. Symonds,J. Denning,L. McNair,S. Arterburn,E. Svarovskaia,D. Moonka,N. Afdhal. Sofosbuvir and ribavirin prevent recurrence of hcv infection after liver transplantation: An open-label study. *Gastroenterology.* 2015. 148:100	Population
7.	X. Forns,S. C. Gordon,E. Zuckerman,E. Lawitz,J. L. Calleja,H. Hofer,C. Gilbert,J. Palcza,A. Y. M.	Intervention

	Howe,M. J. Dinubile,M. N. Robertson,J. Wahl,E. Barr,M. Buti. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. *Journal of hepatology.* 2015. 63:564	
8.	D. Jensen,K. E. Sherman,C. HÃ©zode,S. Pol,S. Zeuzem,V. De Ledinghen,A. Tran,M. Elkhashab,Z. H. Younes,M. Kugelmas,S. Mauss,G. Everson,V. Luketic,J. Vierling,L. Serfaty,M. Brunetto,J. Heo,D. Bernstein,F. McPhee,D. Hennicken,P. Mendez,E. Hughes,S. Noviello. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. *Journal of hepatology.* 2015. 63:30	Population
9.	P. Y. Kwo,P. S. Mantry,E. Coakley,H. S. Te,H. E. Vargas,R. Brown,F. Gordon,J. Levitsky,N. A. Terrault,J. R. Burton,W. Xie,C. Setze,P. Badri,T. Pilot-Matias,R. A. Vilchez,X. Forns. An interferon-free antiviral regimen for HCV after liver transplantation. *New England Journal of Medicine.* 2014. 371:2375	Population
10.	E. Lawitz,F. Poordad,D. M. Brainard,R. H. Hyland,D. An,H. Dvory-Sobol,W. T. Symonds,J. G. Mchutchison,F. E. Membreno. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology.* 2015. 61:769	Population
11.	M. Mandorfer,S. Steiner,P. Schwabl,B. A. Payer,M. C. Aichelburg,G. Lang,K. Grabmeier-Pfistershammer,M. Trauner,M. Peck-Radosavljevic,T. Reiberger. Response-guided boceprevir-based triple therapy in HIV/HCV-coinfected patients: The HIVCOBOC-RGT study. *Journal of Infectious Diseases.* 2015. 211:729	Population
12.	J. -M Molina,C. Orkin,D. M. Iser,F. -X Zamora,M. Nelson,C. Stephan,B. Massetto,A. Gaggar,L. Ni,E. Svarovskaia,D. Brainard,G. M. Subramanian,J. G. McHutchison,M. Puoti,J. K. Rockstroh. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): A multicentre, open-label, non-randomised, phase 3 study. *The Lancet.* 2015. 385:1098	Population
13.	A. Nakagawa,M. Atsukawa,A. Tsubota,N. Shimada,H. Abe,C. Kondo,N. Itokawa,T. Arai,S. Hashimoto,Y. Matsushita,T. Fukuda,K. Nakatsuka,K. Iwakiri,C. Kawamoto,Y. Aizawa,C. Sakamoto. Relationship between HCV dynamics and sustained virological responses in chronic hepatitis C genotype 1b patients treated with telaprevir-based triple therapy. *European Journal of Gastroenterology and Hepatology.* 2014. 26:1329	Intervention
14.	A. S. Lok,D. F. Gardiner,C. Hézode,E. J. Lawitz,M. BourliÃ¨re,G. T. Everson,P. Marcellin,M. Rodriguez-Torres,S. Pol,L. Serfaty,T. Eley,S. -P Huang,J. Li,M. Wind-Rotolo,F. Yu,F. McPhee,D. M. Grasela,C. Pasquinelli. Randomized trial of daclatasvir and asunaprevir with or without PegIFN/RBV for hepatitis C virus genotype 1 null responders. *Journal of hepatology.* 2014. 60:490	Population
15.	A. Osinusi,A. Kohli,M. M. Marti,A. Nelson,X. Zhang,E. G. Meissner,R. Silk,K. Townsend,P. S. Pang,G. M. Subramanian,J. G. McHutchison,A. S. Fauci,H. Masur,S. Kottilil. Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: An open-label pilot study. *Annals of Internal Medicine.* 2014. 161:634	Population
16.	M. Rodriguez-Torres,A. Gaggar,G. Shen,B. Kirby,E. Svarovskaia,D. Brainard,W. T. Symonds,J. G. McHutchison,M. Gonzalez,J. Rodriguez-Orengo. Sofosbuvir for chronic hepatitis C virus infection genotype 1-4 in patients coinfected with HIV. *Journal of acquired immune deficiency syndromes*	Population

	(1999). 2015. 68:543	
17.	K. R. Reddy,S. Zeuzem,F. Zoulim,O. Weiland,A. Horban,C. Stanciu,F. G. Villamil,P. Andreone,J. George,E. Dammers,M. Fu,D. Kurland,O. Lenz,S. Ouwerkerk-Mahadevan,T. Verbinnen,J. Scott,W. Jessner. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): A randomised, double-blind, non-inferiority phase 3 trial. *The Lancet Infectious Diseases.* 2015. 15:27	Population
18.	S. Pol,M. S. Sulkowski,T. Hassanein,E. J. Gane,L. Liu,H. Mo,B. Doehle,B. Kanwar,D. Brainard,G. M. Subramanian,W. T. Symonds,J. G. Mchutchison,R. G. Nahass,M. Bennett,I. M. Jacobson. Sofosbuvir Plus Pegylated Interferon and Ribavirin in Patients With Genotype 1 Hepatitis C Virus in Whom Previous Therapy With Direct-Acting Antivirals Has Failed. *Hepatology.* 2015. 62:129	Population
19.	A. Osinusi,K. Townsend,A. Kohli,A. Nelson,C. Seamon,E. G. Meissner,D. Bon,R. Silk,C. Gross,A. Price,M. Sajadi,S. Sidharthan,Z. Sims,E. Herrmann,J. Hogan,G. Teferi,R. Talwani,M. Proschan,V. Jenkins,D. E. Kleiner,B. J. Wood,G. M. Subramanian,P. S. Pang,J. G. McHutchison,M. A. Polis,A. S. Fauci,H. Masur,S. Kottilil. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIVCo-infection. *JAMA - Journal of the American Medical Association.* 2015. 313:1232	Population
20.	D. Wyles,P. Pockros,G. Morelli,Z. Younes,E. Svarovskaia,J. C. Yang,P. S. Pang,Y. Zhu,J. G. McHutchison,S. Flamm,E. Lawitz. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. *Hepatology.* 2015. 61:1793	Population
21.	M. S. Sulkowski,O. J. Eron,D. Wyles,R. Trinh,J. Lalezari,C. Wang,J. Slim,L. Bhatti,J. Gathe,P. J. Ruane,R. Elion,F. Bredeek,R. Brennan,G. Blick,A. Khatri,K. Gibbons,Y. B. Hu,L. Fredrick,G. Schnell,T. Pilot-Matias,R. Tripathi,B. Da Silva-Tillmann,B. McGovern,A. L. Campbell,T. Podsadecki. Ombitasvir, Paritaprevir Co-dosed with Ritonavir, Dasabuvir, and Ribavirin for Hepatitis C in Patients Co-infected with HIV-1 a Randomized Trial. *JAMA - Journal of the American Medical Association.* 2015. 313:1223	Population
22.	M. S. Sulkowski,S. Naggie,J. Lalezari,W. J. Fessel,K. Mounzer,M. Shuhart,A. F. Luetkemeyer,D. Asmuth,A. Gaggar,L. Ni,E. Svarovskaia,D. M. Brainard,W. T. Symonds,G. M. Subramanian,J. G. McHutchison,M. Rodriguez-Torres,D. Dieterich. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA - Journal of the American Medical Association.* 2014. 312:353	Population
23.	M. S. Sulkowski,K. E. Sherman,D. T. Dieterich,M. Bsharat,L. Mahnke,J. K. Rockstroh,S. Gharakhanian,S. Mccallister,J. Henshaw,P. -M Girard,B. Adiwijaya,V. Garg,R. A. Rubin,M. Adda,V. Soriano. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV a randomized trial. *Annals of Internal Medicine.* 2013. 159:86	Population
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213.	Fontaine H,Lazarus A,Pol S,Pecriaux C,Bagate F,Sultanik P,Boueyre E,Corouge M,Mallet V,Vallet-Pichard A,Sogni P,Duboc D,Cochin Hepatology and Cardiology Group. Bradyarrhythmias Associated with Sofosbuvir Treatment. *New England Journal of Medicine.* 2015. 373:1886	Not a report on intervention
214.	Lomberk M,Klibanov OM. Sofosbuvir (Sovaldi) for hepatitis C virus. *Nurse Practitioner.* 2015. 40:16	Not a report on intervention
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241.	C. S. Graham. Hepatitis C and HIV co-infection: closing the gaps. *JAMA.* 2015. 313:1217	Not a report on intervention
242.	D. M. Evon. Incorporating patient-reported outcomes into hepatitis C virus treatment studies. *Clinical Gastroenterology & Hepatology.* 2014. 12:1360	Not a report on intervention
243.	G. Dusheiko. Controlling hepatitis C with simeprevir. *The Lancet Infectious Diseases.* 2015. 15:2	Not a report on intervention
244.	Stine JG,Cornella S,Shah NL. Treatment of chronic hepatitis C complicated by mixed cryoglobulinemia with new protease inhibitor, sofosbuvir. *Annals of the Rheumatic Diseases.* 2014. 73:e64	Not a report on intervention
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246.	E. Gane. Hepatitis C beware--the end is nigh. *Lancet.* 2014. 384:1557	Not a report on intervention
247.	Eyre NS,Beard MR. HCV NS5A inhibitors disrupt replication factory formation: a novel mechanism of antiviral action. *Gastroenterology.* 2014. 147:959	Not a report on intervention
248.	Backus LI,Belperio PS. Effectiveness research in the evolving HCV landscape. *Digestive Diseases & Sciences.* 2014. 59:2845	Not a report on intervention
249.	Laouenan C,Marcellin P,Lapalus M,Khelifa-Mouri F,Boyer N,Zoulim F,Serfaty L,Bronowicki JP,Martinot-Peignoux M,Lada O,Asselah T,Dorival C,Hezode C,Carrat F,Nicot F,Peytavin G,Mentre F,Guedj J. Using pharmacokinetic and viral kinetic modeling to estimate the antiviral effectiveness of telaprevir, boceprevir, and pegylated interferon during triple therapy in treatment-experienced hepatitis C virus-infected cirrhotic patients. *Antimicrobial Agents &*	Population

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251.	Moorjani H,Koenigsmann C,Kim MJ,Spaulding AC. Prisoners treated for hepatitis C with protease inhibitor, New York, USA, 2012. *Emerging Infectious Diseases.* 2015. 21:186	Intervention
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257.	ClinicalTrials.gov[Internet]. United States of America: A Study to Evaluate the Pharmacokinetic Effect of SCH 503034 (Boceprevir) on Methadone or Buprenorphine/Naloxone Plasma Concentrations (P08123) (NCT01396005); 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Not a report on intervention
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259.	ClinicalTrials.gov[Internet]. United States of America: Boceprevir in Combination With Peginterferon Alfa-2a and Ribavirin in Participants With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin (Study P05685AM2) (NCT00845065): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Population
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262.	ClinicalTrials.gov[Internet]. United States of America: Triple-Therapy in Patients With HCV Genotype 3 Who Previously Failed Treatment (NCT01585584): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Population
263.	ClinicalTrials.gov[Internet]. United States of America: Open-Label Study of Sofusbuvir+Ribavirin With or Without Peginterferon Alfa-2a in Subjects With Chronic HCV Infection Who Participated in Prior Gilead HCV Studies (NCT01625338): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Population
264.	ClinicalTrials.gov[Internet]. United States of America: A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2, 3 and 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Adults (NCT01667731): 2014 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Population
265.	ClinicalTrials.gov[Internet]. United States of America: Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Cirrhotic Subjects With Chronic Genotype 1 HCV Infection (NCT01965535): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Population
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268.	ClinicalTrials.gov[Internet]. United States of America: Single-Dose Pharmacokinetics of BMS-790052 in Participants With Hepatic Impairment (NCT00859053): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Not a report on intervention
269.	ClinicalTrials.gov[Internet]. A Multiple Ascending Dose Study of Daclatasvir (BMS-790052) in Hepatitis C Virus Genotype 1 Infected Subjects (NCT00663208): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Intervention
270.	ClinicalTrials.gov[Internet]. BMS-790052 (Daclatasvir) Plus Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naive Black/African-Americans, Latinos and White/Caucasians With Hepatitis C (NCT01389323): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov.	Intervention
271.	ClinicalTrials.gov[Internet]. Study to Assess the Effect of BMS-790052 on the Pharmacokinetics of Ortho Tri-Cyclen in Healthy Female Subjects (NCT00983957): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Intervention
272.	ClinicalTrials.gov[Internet]. A Single Ascending Dose Study of Daclatasvir (BMS-790052) in Hepatitis C Virus Infected Subjects (NCT00546715): 2015 [cited 2016, March 30]. Available from www.clinicaltrials.gov	Intervention

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STUDIES EXCLUDED AT LEVEL 1 SCREENING (TITLE & ABSTRACT)

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Vargas, C. L., Espinoza, M. A., Giglio, A., and Soza, A.. Cost effectiveness of daclatasvir/asunaprevir versus peginterferon/ribavirin and protease inhibitors for the treatment of hepatitis c genotype 1b Naive patients in Chile. #journal#. 2015. 10:#pages#

Virabhak, S., Yasui, K., Yamazaki, K., Johnson, S., Mitchell, D., Yuen, C., Samp, J. C., and Igarashi, A.. Cost-effectiveness of direct-acting antiviral regimen ombitasvir/paritaprevir/ritonavir in treatment-naive and treatment-experienced patients infected with chronic hepatitis C virus genotype 1b in Japan. #journal#. 2016. #volume#:#pages#

Walker, D. R., Juday, T. R., Manthena, S. R., Jing, Y., and Sood, V.. The impact of ribavirin on real-world adherence rates in hepatitis C patients treated with sofosbuvir plus simeprevir. #journal#. 2015. 7:#pages#

Walker, David R., Pedrosa, Marcos C., Manthena, Shivaji R., Patel, Nikil, and Marx, Steven E.. Early View of the Effectiveness of New Direct-Acting Antiviral (DAA) Regimens in Patients with Hepatitis C Virus (HCV). #journal#. 2015. 32:#pages#

Zeng, Q.-L., Li, C.-X., Zhang, D.-W., Li, W., Xu, G.-H., and Yu, Z.-J.. Letter: Safety and efficacy of sofosbuvir plus daclatasvir with ribavirin for 12 weeks in Chinese treatment-experienced cirrhotic genotype 1b patients with HCV. #journal#. 2016. 43:#pages#

Outcome

(None)

Appendix F

Grading of Recommendations Assessment, Development and Evaluation (GRADE)[20] Assessment and Summary of the Quality of Life (QOL) Results from Each Included Study

GRADE Assessment

After the evidence was synthesised (quantitatively or descriptively), the GHGD science team assessed the strength and quality of the body of evidence available for each outcome of interest using the GRADE approach, which included the results of the Cochrane Risk of Bias evaluations[20].

When assessing the body of evidence for "risk of bias", we found that although all of the RCTs were industry funded (by companies who manufacture DAA-based treatment regimens), effort was taken to guard against the introduction of bias. Examples include having independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving reports; and the use of external independent laboratories. The overall Cochrane Risk of Bias[20] ratings showed little or no risk of bias in the included studies; and for those which did, the direction of the studies was the same. Additionally, for studies that were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA).

The authors of the cost-effectiveness economic model[38] validated the model against the results of empirical natural history studies and prior models and used the results of a meta-analysis as input for some of their key parameters such as SVR rate. However, the data linkages between SVR rates and long-term outcomes (e.g. hepatic mortality) were based on single studies that were not selected through a systematic review of the evidence[38]. Therefore, the body of evidence related to each outcome was rated down for risk of bias.

To assess the body of RCT evidence for "inconsistency" we first examined the level of heterogeneity amongst the included studies[28-32,36,37] based on similarity of point estimates, extent of overlap of confidence intervals, and the $\chi 2$ and I2 statistical tests for heterogeneity. The $\chi 2$ statistic was employed to detect statistical heterogeneity; a statistical significance level was set at p=0.10 as per the Cochrane Handbook[21]. The I2 statistic was used to quantify the magnitude of statistical heterogeneity between studies. Adapting from the Cochrane Handbook[21], we determined that if I2 was 40% or less, we considered heterogeneity to be low and non-important; if I2 was between 41% and 80% we considered heterogeneity to be moderate; and if it was above 80% it was considered high.

If inconsistency was moderate or high, we searched for reasons that could explain the inconsistency. We first used sensitivity analyses to examine heterogeneity. For instance, we tried to explain heterogeneity by the grouping of different treatment regimen(s) (e.g. seeing if removing a specific treatment regimen with outlying results would reduce the overall heterogeneity in outcomes within that drug class). If the sensitivity analyses could not explain the inconsistency, we then assessed whether we believed the inconsistency would reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening. Factors such as whether all studies were on the same side of the line of no effect and whether the differences in results were only between small and large treatment effects (but all in the same direction) helped us to decide whether to rate down for inconsistency or not.

If we could explain heterogeneity, or if heterogeneity could only be partially explained but we felt the level of inconsistency would not impact the CTFPHC's decision to recommend for favour or against screening, we did not rate down for inconsistency. In situations where heterogeneity could not be explained and we believe that the inconsistency would impact the CTFPHC's decision to recommend for or against screening, we rated down for inconsistency.

In situations where only a single study was included for an outcome, we could not evaluate for inconsistency. We judged single-studies to be at high risk for inconsistency regardless of size or how well designed they were since we could not confidently assess whether or not each presented the definitive view of any of the clinical benefits or harms that we examined. However, realizing that inconsistency and imprecision are closely linked, and wanting to avoid penalising the body of evidence twice for a related quality rating, we did not rate the study down for inconsistency if it was already rated down for imprecision.

Following GRADE[20], we included the results of one cost-effectiveness economic modelling study that had the highest methodological quality[38] (based on critical appraisals as described above and consensus by the CTFPHC). This model provided evidence for the greatest number of patient important outcomes by fibrosis score compared to the others[6,39,40]. Despite the differences in methodological quality, the results of this modelling study were somewhat consistent with the other 3 modelling studies identified in our systematic review. Therefore we did not rate down for inconsistency.

Detailed rationale for these decisions related to each outcome is indicated in the GRADE Evidence Profile tables (Appendix G).

When assessing the body of evidence for "indirectness" we found that although the HCV screening status of participants was unknown, they tested positive for HCV, so would be similar to a positive screened population. In an effort to more closely mimic an unscreened population, our PICO stated that for studies to be included, over 80% of the participants need to be treatment-naïve, without HIV or hepatitis B co-infection, without prior liver transplantation, and the majority (over 80%) non-cirrhotic or not show evidence of cirrhosis or liver damage. However, related to the CTFPHC's primary question on the effectiveness of screening, all data is considered to be indirect evidence. This applies to SVR, as well as other patient important outcomes. Additionally, as described elsewhere, the PICO related to this review does not exactly match the screening clinical practice guideline PICO. For these reasons we rated down for indirectness.

In addition to the indirectness related to the question on screening as outlined above, the cost-effectiveness economic model[38] parameters uses epidemiological data from a US health survey as opposed to Canadian sources. In addition, not all input parameters were the result of a systematic search of the evidence and the study accounts for only genotype 1 hepatitis C infection. Although genotype 1 represents the majority of cased found in Canada, it is only a subset of the population of interest for the CTFPHC clinical practice guideline on screening for HCV. Therefore, we rated down the modelling study by two points for indirectness.

To assess the body of evidence (both RCT and modelling outcomes) for "imprecision" we examined 95% confidence intervals (CIs) and compared them to clinical decision thresholds which are based on the results from a Patient Preferences Survey, where patient ranked and provided input on which outcomes were more important in their decision to undergo HCV treatment. Since this systematic review will be used to inform the development of recommendations on screening for hepatitis C, we rated down the quality of the evidence for imprecision if the upper boundary and the lower boundary of a CI would point towards recommending DAA-based regimens over others. In order to inform this assessment, the CTFPHC established a priori clinical decision thresholds for each patient important outcome, which dictated whether the clinical recommendation would be in favour or against treatment with DAA-based regimens (Appendix I).

The optimal information sizes[26] (or minimal number of participants per group – i.e. each for treatment and for control groups) needed for each of the outcomes is provided in Appendix I. Following GRADE[20] methods, we used optimal information size due to the small sample size of some of the studies, particularly for some of the sub-analyses conducted power was likely insufficient to detect statistically significant differences between the DAA group and PR group. The optimal information size is based on a two-sided α=0.05 and desired power of 0.8 and was calculated using http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html[27].

When assessing the body of RCT evidence for "other considerations", due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. For instance, we searched Clinicaltrials.gov[18] for protocols for studies which were registered, but not conducted or reported on and were unable to identify any. Additionally, we did identify one study which was reported on in Clinicaltrials.gov[18], but not published. For these reasons we did not rate down for other considerations (publication bias).

Although we included only one modelling study, our systematic review of the literature identified several modelling studies looking at the outcomes of interest which used data sources from different countries, some with more favourable results than others. Therefore, we believe these studies are representative of the research that is readily available, so, we did not rate down for publication bias.

Specific details pertaining to how we assessed each quality measure can be found in the GRADE Evidence Profile tables associated with this review (Appendix G).

Only outcomes ranked as critical or important by the CTFPHC work group members and/or a focus group comprise of patients, were included in this review and were assessed for quality using the GRADE[20] system. Critical or important outcomes, for which no evidence was identified, are included in the GRADE Evidence Profile tables but do not have any associated rankings.

All data were processed with the GRADEPro software package[25] and presented in table format. The detailed methods that were applied to address the two research questions can be found in the systematic review protocol[14].

Summary of the Quality of Life (QOL) results from each included study

We asked: Do individuals treated with DAA-based regimens have a better quality of life compared to individuals treated with PR alone?

Total number of studies found: 3

Total number of participants: 1,058

Study	**Statistic/Measure** **Quality of life instruments/scales**	**Results**	**Statistical significance**
Scott 2014[33] (n=386) Simeprevir+PR	Difference in PRO[a] between baseline and week 72 follow-up 1) EQ-5D[b] descriptive system 2) EQ-5D Valuation index 3) EQ-5D Visual analogue scale (VAS)	1) Difference in proportion of patients reporting any health problem in the EQ-5D domains DAA vs. PR - Mobility -1.2 0.9 - Self-care 1.2 -1.1 - Usual activities 2.4 6.6 - Pain/discomfort -4.1 5.8 - Anxiety/depression -0.6 2.5 *The proportion of patients with health status problems in any dimension had returned to levels similar to baseline by week 72.* 2) Difference in mean EQ-5D valuation index values (a decrease in value indicates a worsening of health status) DAA vs. PR - Mean value at 72 weeks (approximately) -0.01 -0.01 *Mean EQ-5D valuation index values returned to values similar to those reported at baseline in both groups by week 72.* 3) Difference in mean VAS values (a decrease in value indicates a worsening of health status) DAA vs. PR - Mean value at 72 weeks (approximately) 2.26 -1 *Mean VAS values significantly improved compared to baseline by week 72 in the Simeprevir+PR group only.*	1) Not reported 2) No significant difference 3) Significance was observed in the DAA-based group only.

Wei 2016[34] (n=457) Simeprevir+PR	Difference in PRO[a] between baseline and week 72 follow-up EQ-5D Visual Analogue Scale (VAS)	Difference in least squares(LS) mean for AUC[c] from baseline to week 72 in the Simeprevir(100mg)+PR group versus PR alone LS mean difference vs. PR (95% CI) (97.5% CI) - SIM+PR 152 6233.9 211.8 (4.6-419.1) (6105.6-6362.1) *A statistically significant difference for a change in the AUC from baseline to week 72 favored the Simeprevir+PR group over the PR group.*	p-value versus PR = 0.022
Younossi 2014[35] (n=215) Sofosbuvir+Ribavirin	Difference in Health-related Quality of Life (HRQL) between baseline and 12 weeks post-treatment Short form-36 (SF-36) questionnaire 1) Physical summary scale 2) Mental summary scale	Decrement at 12 weeks post-treatment (negative decrement indicates improvement in HRQL) DAA vs PR (n=105) (n=110) 1) Physical summary scale -1.88 ± 7.95 03 ± 7.02 2) Mental summary scale 0.65 ± 9.24 1.67 ± 9.05 *There were no differences in the HRQL scores in both the physical and mental scales between baseline and 12 weeks post-treatment between the DAA-based and PR only groups.*	p-values: 1) 0.17 2) 0.41

[a] Patient reported outcomes; [b] European Quality of Life 5-Dimensions questionnaire; [c] Area under the plasma concentration-time curve

Appendix G

GRADE[20] Evidence Profile Tables

Table 1.1: GRADE Evidence Profile – DAA-based regimens compared to PR for Hepatitis C in non-pregnant, treatment-naïve adults (BENEFITS)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
SVR12 (Better indicated by higher values)												
7 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	not serious [5]	none [6]	1310/1606 (81.6%)	512/822 (62.3%)	**RR 1.29** (1.22 to 1.37)	**181 more per 1,000** (from 137 more to 230 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR24 (Better indicated by higher values)												
7 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	not serious [7]	none [6]	1302/1606 (81.1%)	503/822 (61.2%)	**RR 1.31** (1.23 to 1.39)	**190 more per 1,000** (from 141 more to 239 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR72 (Better indicated by higher values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
4 [8]	randomised trials	not serious [2]	not serious [9]	serious [4]	not serious [10]	none [6]	923/1135 (81.3%)	295/493 (59.8%)	**RR 1.36** (1.26 to 1.47)	**215 more per 1,000** (from 156 more to 281 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality (all cause) - (Better indicated by lower values)												
5 [11]	randomised trials	not serious [2]	not serious [12]	serious [4]	serious [13]	none [6]	2/1206 (0.2%)	0/644 (0.0%)	**RR 2.14** (0.23 to 20.01)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality (hepatic) - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [18]	none [19]	29756/600000 (5.0%)	10990/100000 (11.0%)	**RR 0.45** (0.44 to 0.46)	**60 fewer per 1,000** (from 59 fewer to 62 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW DAA-based regimens	PR	Relative (95% CI)	Absolute (95% CI)		
Mortality (hepatic) - F0 to F1 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [20]	very serious [17]	not serious [18]	none [19]	59297/1200000 (4.9%)	22251/200000 (11.1%)	**RR 0.44** (0.44 to 0.45)	**62 fewer per 1,000** (from 61 fewer to 62 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F2 to F3 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [21]	none [19]	66113/1200000 (5.5%)	22963/200000 (11.5%)	**RR 0.48** (0.47 to 0.49)	**60 fewer per 1,000** (from 59 fewer to 61 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F4 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [22]	none [19]	76675/600000 (12.8%)	15421/100000 (15.4%)	**RR 0.83** (0.82 to 0.84)	**26 fewer per 1,000** (from 25 fewer to 28 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hepatocellular carcinoma - Modelling - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [23]	none [19]	18456/600000 (3.1%)	4890/100000 (4.9%)	**RR 0.63** (0.61 to 0.65)	**18 fewer per 1,000** (from 17 fewer to 19 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F0 to F1 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [24]	none [19]	36784/1200000 (3.1%)	10068/200000 (5.0%)	**RR 0.61** (0.60 to 0.62)	**20 fewer per 1,000** (from 19 fewer to 20 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F2 to F3 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [25]	none [19]	42575/1200000 (3.5%)	10621/200000 (5.3%)	**RR 0.67** (0.65 to 0.68)	**18 fewer per 1,000** (from 17 fewer to 19 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hepatocellular carcinoma - Modelling - F4 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	serious [26]	none [19]	42926/600000 (7.2%)	7155/100000 (7.2%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [27]	none [19]	12565/600000 (2.1%)	6722/100000 (6.7%)	**RR 0.31** (0.30 to 0.32)	**46 fewer per 1,000** (from 46 fewer to 47 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F0 to F1 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [27]	none [19]	24995/1200000 (2.1%)	13392/200000 (6.7%)	**RR 0.31** (0.30 to 0.32)	**46 fewer per 1,000** (from 46 fewer to 47 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hepatic decompensation - F2 to F3 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [27]	none [19]	26225/1200000 (2.2%)	13608/200000 (6.8%)	**RR 0.32** (0.31 to 0.33)	**46 fewer per 1,000** (from 46 fewer to 47 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F4 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [28]	none [19]	37595/600000 (6.3%)	8911/100000 (8.9%)	**RR 0.70** (0.69 to 0.72)	**27 fewer per 1,000** (from 25 fewer to 28 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [29]	none [19]	1624/600000 (0.3%)	699/100000 (0.7%)	**RR 0.39** (0.35 to 0.42)	**4 fewer per 1,000** (from 4 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Need for liver transplantation - F0 to F1 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [30]	none [19]	3240/1200000 (0.3%)	1269/200000 (0.6%)	**RR 0.43** (0.40 to 0.45)	**4 fewer per 1,000** (from 3 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F2 to F3 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [31]	none [19]	3519/1200000 (0.3%)	1331/200000 (0.7%)	**RR 0.44** (0.41 to 0.47)	**4 fewer per 1,000** (from 4 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F4 - (Better indicated by lower values)												
1 [14]	observational studies	serious [15]	not serious [16]	very serious [17]	not serious [32]	none [19]	4266/600000 (0.7%)	872/100000 (0.9%)	**RR 0.82** (0.76 to 0.88)	**2 fewer per 1,000** (from 1 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (assessed with: European Quality of Life 5-Dimensions (EQ-5D), Health Related Quality of Life (HRQoL), European Quality of Life 5-Dimensions Visual Analogue Scale (EQ-VAS))												
3 [33]	randomised trials	serious [34]	serious [35]	serious [36]	serious [37]	none [38]	Scott (2014): No significant difference (no p-value provided) in the proportion of patients reporting any health problem was observed between the pooled treatment group and control in the European Quality of Life 5-Dimensions (EQ-5D) questionnaire descriptive system. No significant difference (no p-value provided) in mean EQ-5D valuation index values was observed between the pooled treatment group and control. A significant difference (no p-value provided) in mean Visual Analogue Scale values was observed between baseline and week 72 in the pooled treatment group only; Wei (2016) A statistically significant difference (p-value=0.022) for a change in the area under the plasma concentration-time curve from baseline to week 72 was observed in the SIM(100mg)+PR group only and control (211.8, 97.5% CI:4.6-419.1) using the European Quality of Life 5-Dimensions Visual Analogue Scale in favour of the treatment group versus control; Younossi (2014); There were no significant differences in the HRQoL scores of the treatment group and control in both the physical (p-value=0.17) and mental (p-value=0.41) scales between baseline and 12 weeks post-treatment.				⊕◯◯◯ VERY LOW	CRITICAL
Cirrhosis - not reported												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW DAA-based regimens	PR	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-					-	CRITICAL
Improvement in Liver Histology - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Reduced HCV Transmission - not reported												
-	-	-	-	-	-	-					-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Fried 2013; Hayashi, 2014; Jacobson, 2014; Lawitz, 2013-1; Lawitz, 2013-2; Manns, 2014; NCT01725529, 2015.
2. We found that although all of the RCTs were industry funded, effort was taken to guard against the introduction of bias. Examples include independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving the report, and the use of external independent laboratories. The overall Cochrane Risk of Bias ratings showed little or no risk of bias in the included studies, and for those which did, the direction of the studies was the same, or for the ones which were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA). Therefore we did not rate down for risk of bias.
3. There is high heterogeneity observed between the studies (I^2 =81%). The results from Lawitz 2013-1 are likely to be contributing significantly to overall inconsistency as the results from that trial show minimal overlap of confidence intervals with the remaining trials and it has the highest weight (25%). However, we believe it would not reduce the CTFPHC's confidence in the results when deciding to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. Therefore, we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
5. There were more cases of SVR12 reported when treating with DAA as compared with PR (181 more per 1,000). The entire confidence interval of the absolute effect (137 more to 230 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.

6. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).
7. There were more cases of SVR24 reported when treating with DAA as compared with PR (190 more per 1,000). The entire confidence interval of the absolute effect (141 more to 239 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not downgrade for imprecision.
8. Fried 2013; Jacobson, 2014; Manns, 2014; NCT01725529 2015.
9. There is moderate heterogeneity observed between the studies (I^2 =79%). However, we believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. There is also some overlap in confidence intervals. Therefore, we did not rate down for inconsistency.
10. There were more cases of SVR72 reported when treating with DAA as compared with PR (215 more per 1,000). The entire confidence interval of the absolute effect (156 more to 281 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not downgrade for imprecision.
11. Fried 2013; Hayashi, 2014; Jacobson, 2014; Lawitz, 2013-1; Manns, 2014.
12. Heterogeneity is low (I^2 =0%) and confidence intervals are overlapping. Therefore we did not rate down for inconsistency.
13. There was no change in all-cause mortality when treating with DAA as compared with PR (0 fewer per 1,000). The confidence interval of the absolute effect (0 fewer to 0 fewer per 1,000) is narrow and precise. However, the optimal information size was not met. Therefore, we rated down for imprecision.
14. Chahal 2015.
15. The model was validated against results of empirical natural history studies and prior models and the authors used the results of a meta-analysis as input for some of their key parameters such as SVR rate. However, the data linkages between SVR rates and long-term outcomes (e.g. hepatic mortality) were based on single studies that were not selected through the conduct of a systematic review of the evidence. Therefore, we rated down for risk of bias.
16. Following GRADE we included the results of 1 modeling study that had the highest methodological quality (based on critical appraisals and consensus by the CTFPHC). Despite the differences in methodological quality, the results of this modeling study were consistent with the other 3 modeling studies (Dan 2015; Gissel 2015; Wong 2015) identified in our systematic review. Therefore we did not rate down for inconsistency.
17. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Also, the model parameters consider many assumptions and the model uses epidemiological data from a US health survey as opposed to Canadian sources. In addition the study accounts for only genotype 1 hepatitis C infection, which is only a subset of the population of interest for the CTFPHC guideline on screening for HCV. Therefore, we rated down by 2 points for indirectness.
18. There were fewer cases of mortality (hepatic) when treating with DAA as compared with PR (60 fewer per 1,000). The entire confidence interval of the absolute effect (59 fewer to 62 fewer) is to the left of the clinical decision threshold of up to 0 more deaths per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
19. Although we included only 1 modeling study, our systematic review of the literature identified several modeling studies looking at the outcomes of interest, which used data sources from different countries some with more favorable results than others. Therefore, we believe these studies are representative of the research that is readily available, therefore we did not rate down for publication bias (other considerations).
20. There were fewer cases of mortality (hepatic) when treating with DAA as compared with PR (60 fewer per 1,000). The entire confidence interval of the absolute effect (59 fewer to 61 fewer) is to the left of the clinical decision threshold of up to 0 more deaths per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.

21. There were fewer cases of mortality (hepatic) when treating with DAA as compared with PR (62 fewer per 1,000). The entire confidence interval (61 fewer to 62 fewer) is to the left of the clinical decision threshold of up to 0 more deaths per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
22. There were fewer cases of mortality (hepatic) when treating with DAA as compared with PR (26 fewer per 1,000). The entire confidence interval of the absolute effect (25 fewer to 28 fewer) is to the left of the clinical decision threshold of up to 0 more deaths per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
23. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (18 fewer per 1,000). The entire confidence interval of the absolute effect (17 fewer to 19) is to the left of the clinical decision threshold of up to 0 more cases of HCC per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of HCC cases to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
24. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (20 fewer per 1,000). The entire confidence interval of the absolute effect (19 fewer to 20 fewer) is to the left of the clinical decision threshold of up to 0 more cases of HCC per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of HCC cases to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
25. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (18 fewer per 1,000). The entire confidence interval of the absolute effect (17 fewer to 19 fewer) is to the left of the clinical decision threshold of up to 0 more cases of HCC per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of HCC cases to recommend treating with DAA over treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
26. The number of cases of hepatocellular carcinoma for individuals with stage 4 fibrosis was the same when treating with DAA as compared with PR (0 fewer per 1000). However, the confidence interval of the absolute effect (from 1 fewer to 1 more) crosses the threshold of up to 0 more cases per 1,000 treated. In other words, based on the upper boundary of the CI the CTFPHC would recommend against treating with DAA (i.e. the CTFPHC would recommend against if 1 more person per 1000 treated with DAA will develop HCC compared to treating with PR), and based on the lower boundary they would recommend in favour of treating with DAA (i.e. the CTFPHC will recommend in favour if 1 fewer person per 1000 treated with DAA will develop HCC versus PR). Also, the optimal information size was not met. Therefore, we rated down for imprecision.
27. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (46 fewer per 1,000). The entire confidence interval of the absolute effect (46 fewer to 47 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA over treating with PR. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
28. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (27 fewer per 1000). The entire confidence interval of the absolute effect (25 fewer to 28 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA over treating with PR. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
29. There were fewer cases of individuals in need of a liver transplantation when treating with DAA as compared with PR (4 fewer per 1000). The entire confidence interval (4 fewer to 5 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals in need of liver transplantation to recommend treating with DAA over treating with PR. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person is in need of liver transplantation compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
30. There were fewer cases of individuals in need of a liver transplantation when treating with DAA as compared with PR (4 fewer per 1000). The entire confidence interval (3 fewer to 4 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals in need of liver transplantation to recommend treating with DAA over treating with PR. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person is in need of liver transplantation compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.

31. There were fewer cases of individuals in need of a liver transplantation when treating with DAA as compared with PR (4 fewer per 1000). The entire confidence interval (4 fewer to 4 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals in need of liver transplantation to recommend treating with DAA over treating with PR. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person is in need of liver transplantation compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
32. There were fewer cases of individuals in need of a liver transplantation when treating with DAA as compared with PR (2 fewer per 1,000). The entire confidence interval of the absolute effect (1 fewer to 2 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals in need of liver transplantation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person is in need of liver transplantation compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
33. Scott 2014; Wei 2016; Younossi 2014.
34. There was some performance & /or detection bias from lack of or incomplete blinding in 2/3 studies (Scott 2014 and Younossi 2014). Since self-reported quality of life measures are easily influenced by these biases, we rated down for risk of bias.
35. The results are presented in narrative form and could not be pooled due to the fact that various instruments and measures were used. Therefore we rated down for inconsistency.
36. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
37. A meta-analysis was not possible for this outcome due to the fact that various instruments and measures were used. This meant that we could not calculate the absolute effect nor the clinical decision threshold. We did note that the individual study findings crossed the null (no effect) and the difference in effect between the DAA group and control at the last follow-up was small (or crossed the null), meaning that the optimal information size is likely not met. Therefore, we rated down for imprecision.
38. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).

Table 1.2: GRADE[20] Evidence Profile – DAA-based regimens compared to PR for Hepatitis C in non-pregnant, treatment-naïve adults (HARMS)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Anemia (Better indicated by lower values)												
7 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [5]	none [6]	356/1609 (22.1%)	202/822 (24.6%)	**RR 0.83** (0.72 to 0.96)	**42 fewer per 1,000** (from 10 fewer to 69 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Flu-like symptoms (Better indicated by lower values)												
6 [7]	randomised trials	not serious [2]	not serious [8]	serious [4]	serious [9]	none [6]	294/1486 (19.8%)	155/762 (20.3%)	**RR 0.83** (0.70 to 1.00)	**35 fewer per 1,000** (from 0 fewer to 61 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Neutropenia (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW DAA-based regimens**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
7 [1]	randomised trials	not serious [2]	not serious [10]	serious [4]	serious [11]	none [6]	278/1609 (17.3%)	136/822 (16.5%)	**RR 0.90** (0.74 to 1.10)	**17 fewer per 1,000** (from 17 more to 43 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Psychological Adverse Events (Better indicated by lower values)												
7 [1]	randomised trials	not serious [2]	serious [12]	serious [4]	not serious [13]	none [6]	731/10038 (7.3%)	511/5392 (9.5%)	**RR 0.68** (0.61 to 0.77)	**30 fewer per 1,000** (from 22 fewer to 37 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Rash (Better indicated by lower values)												
7 [1]	randomised trials	not serious [2]	serious [14]	serious [4]	serious [15]	none [6]	366/1609 (22.7%)	186/822 (22.6%)	**RR 0.94** (0.80 to 1.10)	**14 fewer per 1,000** (from 23 more to 45 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Withdrawals due to Adverse Events (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW DAA-based regimens	PR	Relative (95% CI)	Absolute (95% CI)		
7 [1]	randomised trials	not serious [2]	not serious [16]	serious [4]	serious [17]	none [6]	20/1609 (1.2%)	41/822 (5.0%)	**RR 0.30** (0.17 to 0.53)	**35 fewer per 1,000** (from 23 fewer to 41 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Fried 2013; Hayashi, 2014; Jacobson, 2014; Lawitz, 2013-1; Lawitz, 2013-2; Manns, 2014; NCT01725529, 2015.
2. We found that although all of the RCTs were industry funded, effort was taken to guard against the introduction of bias. Examples include independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving the report, and the use of external independent laboratories. The overall Cochrane Risk of Bias ratings showed little or no risk of bias in the included studies, and for those which did, the direction of the studies was the same, or for the ones which were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA). Therefore we did not rate down for risk of bias.
3. Heterogeneity is low (I^2 =0%), therefore we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
5. There were fewer cases of anemia reported when treating with DAA as compared with PR (42 fewer per 1,000). The confidence interval of the absolute effect (10 fewer to 69 fewer) is to the left of the clinical threshold of up to 49 more cases of anemia per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of harms if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes).The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.
6. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).
7. Fried 2013; Jacobson, 2014; Lawitz, 2013-1; Lawitz, 2013-2; Manns, 2014; NCT01725529, 2015.
8. Heterogeneity is high (I^2=81%), however sensitivity analysis revealed that when data was limited to trials of DAA+PR regimens (i.e. removed Lawitz 2013-1), heterogeneity was low I^2=5%. Therefore we did not rate down for inconsistency.
9. There were fewer cases of flu-like symptoms reported when treating with DAA as compared with PR (35 fewer per 1,000) The confidence interval of the absolute effect (0 fewer to 61 fewer) is to the left of the clinical threshold of up to 99 more individuals with flu-like symptoms per 1,000 treated, which was established by the CTFPHC as the maximum

acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). However, the optimal information size for this outcome was not met, therefore we downgraded by 1 point for imprecision.

10. Heterogeneity is moderate (I^2=61%), however sensitivity analysis revealed that when data was limited to trials of DAA+PR regimens (i.e. removed Lawitz 2013-1), heterogeneity was low I^2=0%. Therefore we did not rate down for inconsistency.
11. There were fewer cases of neutropenia reported when treating with DAA as compared with PR (17 fewer per 1,000). The entire confidence interval of absolute effect (17 more to 43 fewer) is to the left of the clinical threshold of up to 49 more cases of neutropenia per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). However, the optimal information size for this harm was not met therefore we downgraded by 1 point for imprecision.
12. Heterogeneity is moderate (I^2=80%), and sensitivity analysis removing interferon-free trials (i.e. removed Lawitz 2013-1) did not explain the inconsistencies: I^2=59%. A visual inspection shows that 4 out of the 7 studies (Fried 2013, Jacobson 2014, Lawitz 2013-2, Manns 2014) cross the line of no effect with minimal overlap in confidence intervals. Multiple psychological adverse events were combined for this outcome (i.e. depression, anxiety, etc.) which may be the cause of the heterogeneity observed. However, since inconsistency could not be explained we rated down for inconsistency.
13. There were fewer cases of psychological adverse events reported when treating with DAA as compared with PR (30 fewer per 1,000). The confidence interval of absolute effect (22 fewer to 37 fewer) is to the left of the clinical threshold of up to 49 cases of psychological AEs per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm was also met therefore we did not downgrade for imprecision.
14. Heterogeneity is moderate (I^2=62%), and sensitivity analysis that removed SOF-based trails (i.e. removed Lawitz 2013-1, Lawitz 2013-2) did not explain the inconsistencies: heterogeneity was still moderate I^2=46%. Further, some studies show an effect in favour of DAA and others in favour of PR, with minimal overlap in confidence intervals. Therefore we rated down for inconsistency.
15. There were fewer cases of rash reported when treating with DAA as compared with PR (14 fewer per 1,000). The confidence interval of absolute effect (23 more to 45 fewer) is to the left of the clinical threshold of up to 99 cases of rash per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.
16. Heterogeneity is moderate (I^2=46%), and sensitivity analysis revealed that when limiting to trials of DAA+PR regimens, heterogeneity was low I^2=0%. Therefore, we did not rate down for inconsistency.
17. There were fewer withdrawals due to adverse events reported when treating with DAA as compared with PR (35 fewer per 1,000). The confidence interval (23 fewer to 41 fewer) is to the left of the clinical threshold of up to 49 withdrawals due to AEs per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treating with PR. The rationale is that patients will generally accept higher rates of withdrawals if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we rated down for imprecision.

Table 1.3: GRADE[20] Evidence Profile – SOF+LDV vs. PR be used for Hepatitis C in non-pregnant, treatment-naïve adults

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+LDV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hepatic decompensation (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [5]	none [6]	2005/200000 (1.0%)	6722/100000 (6.7%)	**RR 0.15** (0.14 to 0.16)	**57 fewer per 1,000** (from 56 fewer to 58 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F0 to F1 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [7]	none [6]	3982/400000 (1.0%)	13392/200000 (6.7%)	**RR 0.15** (0.14 to 0.15)	**57 fewer per 1,000** (from 57 fewer to 58 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F2 to F3 (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+LDV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [8]	none [6]	4466/400000 (1.1%)	13608/200000 (6.8%)	**RR 0.16** (0.16 to 0.17)	**57 fewer per 1,000** (from 56 fewer to 57 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F4 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [9]	none [6]	9694/200000 (4.8%)	8911/100000 (8.9%)	**RR 0.54** (0.53 to 0.56)	**41 fewer per 1,000** (from 39 fewer to 42 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [10]	none [6]	5355/200000 (2.7%)	4890/100000 (4.9%)	**RR 0.55** (0.53 to 0.57)	**22 fewer per 1,000** (from 21 fewer to 23 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F0 to F1 (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SOF+LDV	PR	Relative (95% CI)	Absolute (95% CI)		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [11]	none [6]	10661/400000 (2.7%)	10068/200000 (5.0%)	**RR 0.53** (0.52 to 0.54)	**24 fewer per 1,000** (from 23 fewer to 24 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F2 to F3 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [12]	none [6]	12746/400000 (3.2%)	10621/200000 (5.3%)	**RR 0.60** (0.59 to 0.62)	**21 fewer per 1,000** (from 20 fewer to 22 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F4 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	serious [13]	none [6]	13950/200000 (7.0%)	7155/100000 (7.2%)	**RR 0.97** (0.95 to 1.00)	**2 fewer per 1,000** (from 0 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+LDV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [14]	none [6]	351/200000 (0.2%)	699/100000 (0.7%)	**RR 0.25** (0.22 to 0.29)	**5 fewer per 1,000** (from 5 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F0 to F1 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [15]	none [6]	737/400000 (0.2%)	1269/200000 (0.6%)	**RR 0.29** (0.27 to 0.32)	**5 fewer per 1,000** (from 4 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F2 to F3 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [15]	none [6]	829/400000 (0.2%)	1331/200000 (0.7%)	**RR 0.31** (0.29 to 0.34)	**5 fewer per 1,000** (from 4 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F4 (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+LDV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [16]	none [6]	1186/200000 (0.6%)	872/100000 (0.9%)	**RR 0.68** (0.62 to 0.74)	**3 fewer per 1,000** (from 2 fewer to 3 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [17]	none [6]	7142/200000 (3.6%)	10990/100000 (11.0%)	**RR 0.32** (0.32 to 0.33)	**75 fewer per 1,000** (from 74 fewer to 75 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F0 to F1 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [18]	none [6]	14188/400000 (3.5%)	22251/200000 (11.1%)	**RR 0.32** (0.31 to 0.33)	**76 fewer per 1,000** (from 75 fewer to 77 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F2 to F3 (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SOF+LDV	PR	Relative (95% CI)	Absolute (95% CI)		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [19]	none [6]	16687/400000 (4.2%)	22963/200000 (11.5%)	**RR 0.36** (0.36 to 0.37)	**73 fewer per 1,000** (from 72 fewer to 73 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F4 (Better indicated by lower values)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [20]	none [6]	22610/200000 (11.3%)	15241/100000 (15.2%)	**RR 0.74** (0.73 to 0.76)	**40 fewer per 1,000** (from 37 fewer to 41 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Chahal 2015.
2. The model was validated against results of empirical natural history studies and prior models and the authors used the results of a meta-analysis as input for some of their key parameters such as SVR rate. However, the data linkages between SVR rates and long-term outcomes (e.g. hepatic decompensation, hepatocellular carcinoma, need for liver transplantation; and hepatic mortality) were based on single studies that were not selected through the conduct of a systematic review of the evidence. Therefore, we rated down for risk of bias.
3. Following GRADE we included the results of 1 modeling study that had the highest methodological quality (based on critical appraisals and consensus by the CTFPHC). Despite the differences in methodological quality, the results of this modeling study were consistent with the other 3 modeling studies (Dan 2015; Gissel 2015; Wong 2015) identified in our systematic review. Therefore we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Also, the model parameters consider many assumptions and the model uses epidemiological data from a US health survey as opposed to Canadian sources. In addition the study accounts for only

genotype 1 hepatitis C infection, which is only a subset of the population of interest for the CTFPHC guideline on screening for HCV. Therefore, we rated down by 2 points for indirectness.

5. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (57 fewer per 1,000). The entire confidence interval of absolute effect (56 fewer to 58 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
6. Although we included only 1 modeling study, our systematic review of the literature identified several modeling studies looking at the outcomes of interest, which used data sources from different countries some with more favourable results than others. We believe these studies are representative of the research that is readily available, therefore we did not rate down for publication bias (other considerations).
7. There were fewer cases of hepatic decompensation when treating with SOF+PR as compared with PR (57 fewer per 1,000). The entire confidence interval of absolute effect (57 fewer to 58 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
8. There were fewer cases of Hepatic decompensation when treating with SOF+PR as compared with PR (57 fewer per 1,000). The entire confidence interval of absolute effect (56 fewer to 57 fewer) is to the left of the clinical decision threshold of up to 0 case per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
9. There were fewer cases of hepatic decompensation when treating with SOF+PR as compared with PR (41 fewer per 1,000). The entire confidence interval of absolute affect (39 fewer to 42 fewer per 1,000) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
10. There were fewer cases of hepatocellular carcinoma when treating with SOF+PR as compared with PR (22 fewer per 1,000). The entire confidence interval of absolute effect (21 fewer to 23 fewer per 1,000) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatocellular carcinoma to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
11. There were fewer cases of hepatocellular carcinoma when treating with SOF+PR as compared with PR (24 fewer per 1,000). The entire confidence interval of absolute effect (23 fewer to 24 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatocellular carcinoma to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
12. There were fewer cases of hepatocellular carcinoma when treating with SOF+PR as compared with PR (21 fewer per 1,000). The entire confidence interval of absolute effect (20 fewer to 22 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatocellular carcinoma to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. The optimal information size was also met. Therefore, we did not rate down for imprecision.
13. There were fewer cases of hepatocellular carcinoma when treating with SOF+PR as compared with PR (2 fewer per 1,000). The entire confidence interval of absolute effect (0 fewer to 4 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals developing hepatocellular carcinoma to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. However, the optimal information size was not met, therefore we rated down by 1 point for imprecision.
14. There were fewer cases that needed a liver transplantation when treating with SOF+PR as compared with PR (5 fewer per 1,000). The entire confidence interval of absolute effect (5 fewer to 5 fewer per 1,000) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum

acceptable number of individuals that needed a liver transplant to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needed a liver transplant compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.

15. There were fewer cases that needed a liver transplantation when treating with SOF+PR as compared with PR (5 fewer per 1,000). The entire confidence interval (4 fewer to 5 fewer per 1,000) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals needing a liver transplant to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needed a liver transplant compared to treating with PR. In addition, the optimal information size was met; therefore, we did not rate down for imprecision.
16. There were fewer cases that needed a liver transplantation when treating with SOF+PR as compared with PR (3 fewer per 1,000). The entire confidence interval of absolute effect (2 fewer to 3 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals needing a liver transplantation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needing a liver transplantation compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
17. There were fewer cases of mortality (hepatic) when treating with SOF+PR as compared with PR (75 fewer per 1,000). The entire confidence interval of absolute effect (74 fewer to 75 fewer per 1,000) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
18. There were fewer cases of mortality (hepatic) when treating with SOF+PR as compared with PR (76 fewer per 1,000). The entire confidence interval of absolute effect (75 fewer to 77 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
19. There were fewer cases of mortality (hepatic) when treating with SOF+PR as compared with PR (73 fewer per 1,000). The entire confidence interval of absolute effect (72 fewer to 73 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died of hepatic complications compared to treating with PR. The optimal information size was also met, therefore, we did not rate down for imprecision.
20. There were fewer cases of mortality (hepatic) when treating with SOF+PR as compared with PR (40 fewer per 1,000). The entire confidence interval of absolute effect (37 fewer to 41 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of deaths to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died of hepatic complications compared to treating with PR. In addition, the optimal information size was also met; therefore, we did not rate down for imprecision.

Table 1.4: GRADE[20] Evidence Profile – SIM+PR vs. PR be used for Hepatitis C in non-pregnant, treatment-naïve adults

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SIM+PR**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
SVR12 (Better indicated by higher values)												
5 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	not serious [5]	none [6]	1054/1258 (83.8%)	335/553 (60.6%)	**RR 1.38** (1.29 to 1.48)	**230 more per 1,000** (from 176 more to 291 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR12 - F0 to F2 (Better indicated by higher values)												
2 [7]	randomised trials	not serious [2]	not serious [8]	serious [4]	not serious [9]	none [6]	317/378 (83.9%)	106/192 (55.2%)	**RR 1.52** (1.33 to 1.74)	**287 more per 1,000** (from 182 more to 409 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR12 - F3 to F4 (Better indicated by higher values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SIM+PR	PR	Relative (95% CI)	Absolute (95% CI)		
2 [7]	randomised trials	not serious [2]	not serious [10]	serious [4]	not serious [11]	none [6]	89/130 (68.5%)	26/72 (36.1%)	**RR 1.91** (1.37 to 2.66)	**329 more per 1,000** (from 134 more to 599 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR24 (Better indicated by higher values)												
5 [1]	randomised trials	not serious [2]	not serious [12]	serious [4]	not serious [13]	none [6]	1050/1258 (83.5%)	329/553 (59.5%)	**RR 1.40** (1.31 to 1.51)	**238 more per 1,000** (from 184 more to 303 more)	⊕⊕⊕◯ MODERATE	CRITICAL
SVR24 - F0 to F2 (Better indicated by higher values)												
1 [14]	randomised trials	not serious [2]	not serious [15]	serious [4]	serious [16]	none [6]	218/262 (83.2%)	45/70 (64.3%)	**RR 1.29** (1.08 to 1.55)	**186 more per 1,000** (from 51 more to 354 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SIM+PR**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
SVR24 - F3 to F4 (Better indicated by higher values)												
1 [14]	randomised trials	not serious [2]	not serious [15]	serious [4]	serious [17]	none [6]	31/46 (67.4%)	5/7 (71.4%)	**RR 0.94** (0.57 to 1.57)	**43 fewer per 1,000** (from 307 fewer to 407 more)	⊕⊕◯◯ LOW	CRITICAL
SVR72 (Better indicated by higher values)												
4 [18]	randomised trials	not serious [2]	not serious [19]	serious [4]	not serious [20]	none [6]	923/1135 (81.3%)	295/493 (59.8%)	**RR 1.36** (1.26 to 1.47)	**215 more per 1,000** (from 156 more to 281 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Anemia (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SIM+PR**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
5 [1]	randomised trials	not serious [2]	not serious [21]	serious [4]	serious [22]	none [6]	316/1258 (25.1%)	167/553 (30.2%)	**RR 0.85** (0.73 to 1.00)	**45 fewer per 1,000** (from 0 fewer to 82 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Flu-like symptoms (Better indicated by lower values)												
4 [18]	randomised trials	not serious [2]	not serious [23]	serious [4]	serious [24]	none [6]	265/1135 (23.3%)	109/493 (22.1%)	**RR 0.99** (0.82 to 1.20)	**2 fewer per 1,000** (from 40 fewer to 44 more)	⊕⊕◯◯ LOW	IMPORTANT
Neutropenia (Better indicated by lower values)												
5 [1]	randomised trials	not serious [2]	not serious [25]	serious [4]	serious [26]	none [6]	255/1258 (20.3%)	101/553 (18.3%)	**RR 1.08** (0.88 to 1.33)	**15 more per 1,000** (from 22 fewer to 60 more)	⊕⊕◯◯ LOW	IMPORTANT
Psychological Adverse Events (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SIM+PR**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
5 [1]	randomised trials	not serious [2]	serious [27]	serious [4]	serious [28]	none [6]	569/6718 (8.5%)	287/2754 (10.4%)	**RR 0.80** (0.70 to 0.92)	**21 fewer per 1,000** (from 8 fewer to 31 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Rash (Better indicated by lower values)												
5 [1]	randomised trials	not serious [2]	not serious [29]	serious [4]	serious [30]	none [6]	314/1258 (25.0%)	139/553 (25.1%)	**RR 1.00** (0.85 to 1.19)	**0 fewer per 1,000** (from 38 fewer to 48 more)	⊕⊕◯◯ LOW	IMPORTANT
Withdrawals due to Adverse Events (Better indicated by lower values)												
5 [1]	randomised trials	not serious [2,31]	not serious [32]	not serious [4]	serious [33]	none [6]	16/1258 (1.3%)	10/553 (1.8%)	**RR 0.73** (0.35 to 1.53)	**5 fewer per 1,000** (from 10 more to 12 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Fried 2013; Hayashi, 2014; Jacobson, 2014; Manns, 2014; NCT01725529, 2015;

2. We found that although all of the RCTs were industry funded, effort was taken to guard against the introduction of bias. Examples include independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving the report, and the use of external independent laboratories. The overall Cochrane Risk of Bias ratings showed little or no risk of bias in the included studies, and for those which did, the direction of the studies was the same, or for the ones which were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA). Therefore we did not rate down for risk of bias.
3. Heterogeneity is moderate (I^2=76%). The results from NCT01725529 2015 are likely contributing significantly to overall heterogeneity as the results from that trial show minimal overlap of confidence intervals with the remaining trials and it has the highest weight (33.4%). However, we believe the current imprecision would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. There is also some overlap in confidence intervals. Therefore, we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
5. There were more cases of SVR12 reported when treating with DAA as compared with PR (230 more per 1,000). The entire confidence interval of absolute effect (176 more to 291 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
6. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).
7. Jacobson, 2104; Manns, 2014;
8. Inconsistency is moderate (I^2=43%). However, we believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. There is also some overlap in confidence intervals. Therefore, we did not rate down for inconsistency.
9. There were more cases of SVR12 reported when treating with DAA as compared with PR (287 more per 1,000). The entire confidence interval of absolute effect (182 more to 409 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
10. Inconsistency is moderate (I^2=69%). However, we believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. There is also some overlap in confidence intervals. Therefore, we did not rate down for inconsistency.
11. There were more cases of SVR12 reported when treating with DAA as compared with PR (329 more per 1,000). The entire confidence interval of absolute effect (134 more to 599 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not downgrade for imprecision.
12. Heterogeneity is moderate (I^2=76%), with minimal overlap in confidence interval of the NCT01725529 2015 trial (weight 33.7%) with the remaining studies. However, we believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. Therefore, we did not rate down for inconsistency.
13. There were more cases of SVR24 reported when treating with DAA as compared with PR (238 more per 1,000). The entire confidence interval of absolute effect (184 more to 303 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not downgrade for imprecision.
14. Fried 2013.

15. In this situation the assessment of inconsistency is based on a single study. However, we considered the inconsistency of relative treatment effect to be non-significant (i.e. our confidence in the results was not reduced). Therefore, we did not downgrade for inconsistency.
16. There were more cases of SVR24 reported when treating with DAA as compared with PR (186 more per 1,000). The entire confidence interval of absolute effect (51 more to 354 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. However, the optimal information size was not met. Therefore, we downgraded by 1 point for imprecision.
17. There were fewer cases of SVR24 reported for individuals with F3 to F4 when treating with DAA as compared with PR (43 fewer per 1,000). The confidence interval of absolute effect (307 fewer to 407 more) crosses the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In other words based on the upper boundary (407 more) the CTFPHC will recommend in favour of treating with the DAA, but based on the lower boundary (307 fewer) the CTFPHC would recommend against, which demonstrates imprecision. In addition, the optimal information size was not met. Therefore, we downgraded by 1 point for imprecision.
18. Fried 2013; Jacobson, 2014; Manns, 2014; NCT01725529 2015.
19. Heterogeneity is moderate (I^2=76%), with minimal overlap in confidence interval of the NCT01725529 2015 trial (weight 37.5%) with the remaining studies. However, we believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that all studies are on the same side of the line of no effect and the differences in results are between small and large treatment effects. Therefore, we did not rate down for inconsistency.
20. There were more cases of SVR72 reported when treating with DAA as compared with PR (214 more per 1,000). The entire confidence interval of absolute effect (156 more to 281 more) is to the right of the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated with DAA, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treating with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In addition, the optimal information size was met. Therefore, we did not downgrade for imprecision.
21. Heterogeneity is low (I^2 =0%) and confidence intervals are overlapping. Therefore we did not rate down for inconsistency.
22. There were fewer cases of anemia reported when treating with SIM+PR as compared with PR (45 fewer per 1,000). The confidence interval of absolute effect (0 fewer to 82 fewer) is to the left of the clinical threshold of up to 49 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.
23. Heterogeneity is low (I^2 =0%) and confidence intervals are overlapping. Therefore we did not rate down for inconsistency.
24. There were fewer cases of flu like symptoms reported when treating with SIM+PR as compared with PR (2 fewer per 1,000). The entire confidence interval of absolute effect (40 fewer to 44 more) is to the left of the clinical threshold of up to 99 cases more per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met, therefore, we downgraded by 1 point for imprecision.
25. Heterogeneity is low (I^2 =0%) and confidence intervals are overlapping. Therefore we did not rate down for inconsistency.
26. There were more cases of neutropenia reported when treating with SIM+PR as compared with PR (15 more per 1,000). The confidence interval (22 fewer to 60 more) crosses the clinical threshold of up to 49 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR .The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes).. In other words based on the upper boundary (60 more cases) the CTFPHC would recommend against treating with the DAA, but based on the lower boundary (22 fewer cases) the CTFPHC would recommend in favour, which demonstrates imprecision. The optimal information size for this harm was also not met therefore we downgraded by 1 point for imprecision.
27. Heterogeneity is moderate (I^2=67%). A visual inspection shows that 3 out of the 5 studies (Fried 2013, Jacobson 2014, Manns 2014) cross the line of no effect. We believe this inconsistency may reduce the CTFPHC's confidence in the results when deciding to recommend for or against screening. Although, multiple psychological adverse events were

combined for this outcome (i.e. depression, anxiety, etc.) and may be the cause of the heterogeneity observed. Since inconsistency could not be explained we rated down for inconsistency.

28. There were fewer psychological adverse events reported when treating with SIM+PR as compared with PR (21 fewer per 1,000). The confidence interval of absolute effect (8 fewer to 31 fewer) is to the left of the clinical threshold of up to 49 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm was not met however therefore we downgraded by 1 point for imprecision.
29. Heterogeneity is moderate (I^2=46%). We believe it would not reduce the CTFPHC's confidence in the results when deciding whether to recommend for or against screening given that a visual inspection shows that 4 out of the 5 studies (Fried 2013, Jacobson 2014, Manns 2014, NCT017255292015) cross the line of no effect. Therefore, we did not rate down for inconsistency.
30. There were fewer cases of rash reported when treating with SIM+PR as compared with PR (0 fewer per 1,000). The confidence interval of absolute effect (38 fewer to 48 more) is to the left of the clinical threshold of up to 99 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met hence we downgraded by one point for imprecision.
31. One study (NCT01725529 2015) was subject to other biases. Therefore we downgraded by 0.5 for risk of bias as this bias could have influenced this outcome and transferred 0.5 from publication bias (other considerations).
32. Heterogeneity is low (I^2 =0%) and confidence intervals are overlapping. Therefore, we did not rate down for inconsistency.
33. There were fewer withdrawals due to AEs when treating with SIM+PR as compared with PR (5 fewer per 1,000). The confidence interval of absolute effect (38 fewer to 48 more) is to the left of the clinical threshold of up to 49 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.

Table 1.5: GRADE[20] Evidence Profile – SOF+PR vs. PR be used for Hepatitis C in non-pregnant, treatment-naïve adults

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+PR**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
SVR12 (Better indicated by higher values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [5]	none [6]	86/95 (90.5%)	15/26 (57.7%)	**RR 1.57** (1.12 to 2.19)	**329 more per 1,000** (from 69 more to 687 more)	⊕⊕◯◯ LOW	CRITICAL
SVR24 (Better indicated by higher values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [7]	none [6]	83/95 (87.4%)	15/26 (57.7%)	**RR 1.51** (1.08 to 2.12)	**294 more per 1,000** (from 46 more to 646 more)	⊕⊕◯◯ LOW	CRITICAL
Anemia (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SOF+PR	PR	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [8]	none [6]	19/95 (20.0%)	7/26 (26.9%)	**RR 0.74** (0.35 to 1.57)	**70 fewer per 1,000** (from 153 more to 175 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Flu-like symptoms (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [9]	none [6]	22/95 (23.2%)	2/26 (7.7%)	**RR 3.01** (0.76 to 11.98)	**155 more per 1,000** (from 18 fewer to 845 more)	⊕⊕◯◯ LOW	IMPORTANT
Neutropenia (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [10]	none [6]	23/95 (24.2%)	5/26 (19.2%)	**RR 1.26** (0.53 to 2.99)	**50 more per 1,000** (from 90 fewer to 383 more)	⊕⊕◯◯ LOW	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SOF+PR	PR	Relative (95% CI)	Absolute (95% CI)		
Psychological Adverse Events (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [11]	none [6]	70/760 (9.2%)	26/208 (12.5%)	**RR 0.74** (0.48 to 1.13)	**33 fewer per 1,000** (from 16 more to 65 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Rash (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [12]	none [6]	29/95 (30.5%)	4/26 (15.4%)	**RR 1.98** (0.77 to 5.14)	**151 more per 1,000** (from 35 fewer to 637 more)	⊕⊕◯◯ LOW	IMPORTANT
Withdrawals due to Adverse Events (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [13]	none [6]	1/95 (1.1%)	2/26 (7.7%)	**RR 0.14** (0.01 to 1.45)	**66 fewer per 1,000** (from 35 more to 76 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Lawitz, 2013-2.
2. We found that although all of the RCTs were industry funded, effort was taken to guard against the introduction of bias. Examples include independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving the report, and the use of external independent laboratories. The overall Cochrane Risk of Bias ratings showed little or no risk of bias in the included studies, and for those which did, the direction of the studies was the same, or for the ones which were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA). Therefore we did not rate down for risk of bias.
3. In this situation the assessment of inconsistency is based on a single study. However, we considered the inconsistency of relative treatment effect to be non-significant (i.e. our confidence in the results was not reduced). Thus, we did not downgrade for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
5. There were more cases of SVR12 reported when treating with DAA as compared with PR (329 more per 1,000). The entire confidence interval of absolute effect (69 more to 687 more) is to the right of the clinical threshold of up to 49 fewer individuals achieving SVR per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treatment with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. However, the optimal information size was not met. Therefore, we rated down for imprecision.
6. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).
7. There were more cases of SVR24 reported when treating with DAA as compared with PR (294 more per 1,000). The entire confidence interval of absolute effect (46 more to 646 more) is to the right of the clinical threshold of up to 49 fewer individuals achieving SVR per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals not achieving SVR to recommend treating with DAA over treatment with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. However, the optimal information size was not met. Therefore, we rated down for imprecision.
8. There were fewer cases of anemia reported when treating with SOF+PR as compared with PR (70 fewer per 1,000). However the confidence interval of absolute effect (153 more to 175 fewer) crosses the clinical decision threshold of up to 49 more cases of anemia per 1,000 treated established by CTFPHC to recommend in favour of treating with DAA. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). In other words, based on the upper boundary (153 more cases) the CTFPHC would recommend against treating with the DAA, but based on the lower boundary (175 fewer cases) the CTFPHC would recommend in favour, which demonstrates imprecision. Furthermore, the optimal information size was also not met. Therefore we rated down for imprecision.
9. There were more cases of flu-like symptoms reported when treating with SOF+PR as compared with PR (155 more per 1,000). However, the confidence interval of absolute effect (845 more to 18 fewer) crosses the clinical decision threshold of up to 99 more individuals reporting flu-like symptoms per 1,000 treated, which was established by CTFPHC as the maximum number of individuals with flu-like symptoms to recommend treating with DAA over PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). In other words, based on the upper boundary (845 more cases) the CTFPHC would recommend against treating with the DAA, but based on the lower boundary (18 fewer cases) the CTFPHC would recommend in favour, which demonstrates imprecision. In addition, the optimal information size was also not met. Therefore we downgraded by 1 point for imprecision.
10. There were more cases of neutropenia reported when treating with SOF+PR as compared with PR (50 more per 1,000). The confidence interval of absolute effect (383 more to 90 fewer) crosses the clinical decision threshold of up to 49 more cases of neutropenia per 1,000 treated, which was established by CTFPHC as the maximum number of neutropenia cases to recommend treating with DAA over PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). In other words, based on the upper boundary (383 more cases) the CTFPHC would recommend against treating with the DAA, but based on the lower boundary (90 fewer cases) the CTFPHC would recommend in favour, which demonstrates imprecision. In addition, the optimal information size was also not met. Therefore we downgraded by 1 point for imprecision.

11. There were fewer psychological adverse events reported when treating with SOF+PR as compared with PR. The confidence interval (65 fewer to 16 more per 1,000) is to the left of the clinical threshold of up to 49 more cases of psychological adverse events per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.
12. There were more cases of rash reported when treating with SOF+PR as compared with PR (151 more per 1,000). The confidence interval of absolute effect (637 more to 35 fewer) crosses the clinical decision threshold of up to 99 more cases of rash per 1,000 treated, which was established by CTFPHC as the maximum number of rash cases to recommend treating with DAA over treating with PR. In other words, based on the upper boundary (637 more cases) the CTFPHC would recommend against treating with the DAA, but based on the lower boundary (35 fewer cases) the CTFPHC would recommend in favour, which demonstrates imprecision. In addition, the optimal information size for this outcome was not met; therefore we downgraded by 1 point for imprecision.
13. There were fewer withdrawals due to AEs reported when treating with SOF+PR as compared with PR (66 fewer per 1,000). The confidence interval of absolute affect (76 fewer to 35 more) is to the left of the clinical threshold of up to 49 more withdrawals due to AEs per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of withdrawals due to AEs to recommend treating with DAA over treatment with PR. The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.

Table 1.6: GRADE[20] Evidence Profile – SOF+RBV vs. PR be used for Hepatitis C in non-pregnant, treatment-naïve adults

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+RBV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
SVR12 (Better indicated by higher values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [5]	none [6]	170/253 (67.2%)	162/243 (66.7%)	**RR 1.01** (0.89 to 1.14)	**7 more per 1,000** (from 73 fewer to 93 more)	⊕⊕◯◯ LOW	CRITICAL
SVR24 (Better indicated by higher values)												
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [7]	none [6]	169/253 (66.8%)	159/243 (65.4%)	**RR 1.02** (0.90 to 1.16)	**13 more per 1,000** (from 65 fewer to 105 more)	⊕⊕◯◯ LOW	CRITICAL
Anemia (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+RBV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	not serious [2]	not serious [3]	serious [4]	serious [8]	none [6]	21/256 (8.2%)	28/243 (11.5%)	**RR 0.71** (0.42 to 1.22)	**33 fewer per 1,000** (from 25 more to 67 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Flu-like symptoms (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	serious [9]	serious [4]	not serious [10]	none [6]	7/256 (2.7%)	44/243 (18.1%)	**RR 0.15** (0.07 to 0.33)	**154 fewer per 1,000** (from 121 fewer to 168 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Neutropenia (Better indicated by lower values)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW SOF+RBV**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	randomised trials	not serious [2]	serious [9]	serious [4]	not serious [11]	none [6]	0/256 (0.0%)	30/243 (12.3%)	**RR 0.02** (0.00 to 0.25)	**121 fewer per 1,000** (from 93 fewer to 121 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Psychological Adverse Events (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	serious [9]	serious [4]	not serious [12]	none [6]	92/2560 (3.6%)	198/2430 (8.1%)	**RR 0.44** (0.35 to 0.56)	**46 fewer per 1,000** (from 36 fewer to 53 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Rash (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	serious [9]	serious [4]	not serious [13]	none [6]	23/256 (9.0%)	43/243 (17.7%)	**RR 0.51** (0.32 to 0.82)	**87 fewer per 1,000** (from 32 fewer to 120 fewer)	⊕⊕◯◯ LOW	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW SOF+RBV	PR	Relative (95% CI)	Absolute (95% CI)		
Withdrawals due to Adverse Events (Better indicated by lower values)												
1 [1]	randomised trials	not serious [2]	serious [9]	serious [4]	not serious [14]	none [6]	3/256 (1.2%)	29/243 (11.9%)	**RR 0.10** (0.03 to 0.32)	**107 fewer per 1,000** (from 81 fewer to 116 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. Lawitz, 2013-1.
2. We found that although all of the RCTs were industry funded, effort was taken to guard against the introduction of bias. Examples include independent individuals with no financial benefit from the sponsor conducting the study, doing the data analysis, writing and approving the report, and the use of external independent laboratories. The overall Cochrane Risk of Bias ratings showed little or no risk of bias in the included studies, and for those which did, the direction of the studies was the same, or for the ones which were identified as potentially biased, the direction of the effect was not to the benefit of the sponsor (e.g. the effect was towards PR and not DAA). Therefore we did not rate down for risk of bias.
3. Due to not have a body of evidence to examine, we were unable to directly evaluate inconsistency and we could not be certain that a single study, regardless of its size or how well designed it is, presented the definitive view of any of the clinical benefits or harms that we are examining. Accordingly, we judged single-studies to be at high risk for inconsistency, but with the caveat that if we had already rated down for imprecision (because the OIS was not met), then we did don't rate down again for inconsistency. This measure was to avoid penalising the body of evidence twice for a related quality rating. In this instance OIS was met and we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Therefore we rated down for indirectness.
5. There were more cases of SVR12 reported when treating with DAA as compared with PR (7 more per 1,000). However the confidence interval of absolute effect (93 more to 73 fewer) crosses the clinical decision threshold of up 49 fewer individuals achieving SVR per 1,000 treated established by CTFPHC as the maximum number of individuals not achieving SVR in order to recommend treating with DAA over treatment with PR. The rationale is that the slightly lower SVR rates would be offset by the improved tolerability of the DAA-regimen. In other words, based on the upper boundary (93 more cases) the CTFPHC will recommend in favour of treating with the DAA, but based on the lower boundary (73 fewer cases) the CTFPHC would recommend against, which demonstrates imprecision. In addition, the optimal information size was not met. Therefore, we downgraded by 1 point for imprecision.

6. Due to the small number of included studies per outcome we were unable to assess for publication bias using funnel plots. However we believe that the studies found are representative of the literature available. Additionally, we searched for protocols for which no studies were found, but did not identify any. For these reasons we did not rate down for other considerations (publication bias).
7. There were more cases of SVR24 reported when treating with DAA as compared with PR (13 more per 1,000). However the confidence interval of absolute effect (105 more to 65 fewer) crosses the clinical decision threshold of up to 49 fewer individuals achieving SVR per 1,000 treated established by CTFPHC as the maximum number of individuals not achieving SVR to recommend treatment with DAA over treatment with PR. In other words, based on the upper boundary (105 more) cases the CTFPHC will recommend in favour of treating with the DAA, but based on the lower boundary (65 fewer cases) the CTFPHC would recommend against, which demonstrates imprecision. In addition, the optimal information size was not met. Therefore, we downgraded by 1 point for imprecision.
8. There were fewer cases of anemia reported when treating with SOF+RBV as compared with PR (33 fewer per 1,000). The confidence interval of absolute effect (67 fewer to 25 more) is to the left of the clinical threshold of up to 49 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm however was not met therefore we downgraded by 1 point for imprecision.
9. Due to not have a body of evidence to examine, we were unable to directly evaluate inconsistency and we could not be certain that a single study, regardless of its size or how well designed it is, presented the definitive view of any of the clinical benefits or harms that we are examining. Accordingly, we judged single-studies to be at high risk for inconsistency, but with the caveat that if we had already rated down for imprecision (because the OIS was not met), then we did don't rate down again for inconsistency. This measure was to avoid penalising the body of evidence twice for a related quality rating. In this instance OIS was not met and we rated down for inconsistency.
10. There were fewer cases of flu like symptoms reported when treating with SOF+RBV as compared with PR (153 fewer per 1,000). The entire confidence interval of absolute effect (121 fewer to 168 fewer) is to the left of the clinical threshold of up to 99 more cases of flu-like symptoms per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm was also met therefore we did not downgrade for imprecision.
11. There were fewer cases of neutropenia reported when treating with SOF+RBV as compared with PR (121 fewer per 1,000). The confidence interval of absolute affect (93 fewer to 121 fewer) is to the left of the clinical threshold of up to 49 more cases of neutropenia per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of neutropenia cases to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of harms, if it results in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm was also met therefore we did not downgrade for imprecision.
12. There were fewer psychological adverse events reported when treating with SOF+RBV as compared with PR (46 fewer per 1,000). The confidence interval of absolute affect (36 fewer to 53 fewer) is to the right of the clinical threshold of 49 more psychological adverse events per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The rationale is that patients will generally accept higher rates of adverse events if it resulted in a higher rate of SVR (and a likely reduction in clinical important outcomes). The optimal information size for this harm was also met therefore we did not downgraded imprecision.
13. There were fewer cases of rash reported when treating with SOF+RBV as compared with PR (87 fewer per 1,000). The confidence interval of absolute effect (32 fewer to 120 fewer) is to the left of the clinical threshold of up to 99 more cases of rash per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The optimal information size for this harm was also met therefore we did not downgrade for imprecision.
14. There were fewer withdrawals due to AEs reported when treating with SOF+RBV as compared with PR (107 fewer per 1,000). The confidence interval of absolute effect (81 fewer to 116 fewer) is to the left of the clinical threshold of up to 49 more withdrawals per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this harm to recommend treating with DAA over treatment with PR. The optimal information size for this harm was also met therefore we did not downgrade for imprecision.

Table 1.7: GRADE[20] Evidence Profile – OMB/PAR/RIT+DAS (+/-RBV) vs. PR be used for Hepatitis C in non-pregnant, treatment-naïve adults

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW OMB/PAR/RIT+DAS (+/-RBV)	PR	Relative (95% CI)	Absolute (95% CI)		
Hepatic decompensation												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [5]	none [6]	1186/100000 (1.2%)	6722/100000 (6.7%)	**RR 0.18** (0.17 to 0.19)	**55 fewer per 1,000** (from 54 fewer to 56 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F0 to F1												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [7]	none [6]	2362/200000 (1.2%)	13392/200000 (6.7%)	**RR 0.18** (0.17 to 0.18)	**55 fewer per 1,000** (from 55 fewer to 56 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F2 to F3												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW OMB/PAR/RIT+DAS (+/-RBV)**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [5]	none [6]	2578/200000 (1.3%)	13608/200000 (6.8%)	**RR 0.19** (0.18 to 0.20)	**55 fewer per 1,000** (from 54 fewer to 56 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatic decompensation - F4												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [8]	none [6]	5277/100000 (5.3%)	8911/100000 (8.9%)	**RR 0.59** (0.57 to 0.61)	**37 fewer per 1,000** (from 35 fewer to 38 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [9]	none [6]	2701/100000 (2.7%)	4890/100000 (4.9%)	**RR 0.55** (0.53 to 0.58)	**22 fewer per 1,000** (from 21 fewer to 23 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F0 to F1												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NEW OMB/PAR/RIT+DAS (+/-RBV)	PR	Relative (95% CI)	Absolute (95% CI)		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [10]	none [6]	5397/200000 (2.7%)	10068/200000 (5.0%)	**RR 0.54** (0.52 to 0.55)	**23 fewer per 1,000** (from 23 fewer to 24 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F2 to F3												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [11]	none [6]	6422/200000 (3.2%)	10621/200000 (5.3%)	**RR 0.60** (0.59 to 0.62)	**21 fewer per 1,000** (from 20 fewer to 22 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Hepatocellular carcinoma - Modelling - F4												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	serious [12]	none [6]	6876/100000 (6.9%)	7155/100000 (7.2%)	**RR 0.96** (0.93 to 0.99)	**3 fewer per 1,000** (from 1 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW OMB/PAR/RIT+DAS (+/-RBV)**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [13]	none [6]	185/100000 (0.2%)	699/100000 (0.7%)	**RR 0.26** (0.23 to 0.31)	**5 fewer per 1,000** (from 5 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F0 to F1												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [14]	none [6]	384/200000 (0.2%)	1269/200000 (0.6%)	**RR 0.30** (0.27 to 0.34)	**4 fewer per 1,000** (from 4 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F2 to F3												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	serious [15]	none [6]	435/200000 (0.2%)	1331/200000 (0.7%)	**RR 0.33** (0.29 to 0.36)	**4 fewer per 1,000** (from 4 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Need for liver transplantation - F4												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW OMB/PAR/RIT+DAS (+/-RBV)**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [16]	none [6]	572/100000 (0.6%)	872/100000 (0.9%)	**RR 0.66** (0.59 to 0.73)	**3 fewer per 1,000** (from 2 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic)												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [17]	none [6]	3751/100000 (3.8%)	10990/100000 (11.0%)	**RR 0.34** (0.33 to 0.35)	**73 fewer per 1,000** (from 71 fewer to 74 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F0 to F1												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [18]	none [6]	7490/200000 (3.7%)	22251/200000 (11.1%)	**RR 0.34** (0.33 to 0.35)	**73 fewer per 1,000** (from 72 fewer to 75 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F2 to F3												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NEW OMB/PAR/RIT+DAS (+/-RBV)**	**PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [19]	none [6]	8668/200000 (4.3%)	22963/200000 (11.5%)	**RR 0.38** (0.37 to 0.39)	**71 fewer per 1,000** (from 70 fewer to 72 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (hepatic) - F4												
1 [1]	observational studies	serious [2]	not serious [3]	very serious [4]	not serious [20]	none [6]	11595/100000 (11.6%)	15241/100000 (15.2%)	**RR 0.76** (0.74 to 0.78)	**37 fewer per 1,000** (from 34 fewer to 40 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Chahal 2015.
2. The model was validated against results of empirical natural history studies and prior models and the authors used the results of a meta-analysis as input for some of their key parameters such as SVR rate. However, the data linkages between SVR rates and long-term outcomes (e.g. hepatic decompensation, hepatocellular carcinoma, need for liver transplantation; and hepatic mortality) were based on single studies that were not selected through the conduct of a systematic review of the evidence. Therefore we rated down for risk of bias.
3. Following GRADE we included the results of 1 modeling study that had the highest methodological quality (based on critical appraisals and consensus by the CTFPHC). Despite the differences in methodological quality, the results of this modeling study were consistent with the other 3 modeling studies (Dan 2015; Gissel 2015; Wong 2015) identified in our systematic review. Therefore, we did not rate down for inconsistency.
4. This systematic review presents indirect evidence to answer the CTFPHC's question on the effectiveness of screening for HCV. The results of this systematic review will be used, along with other evidence, to help ascertain long term and other clinically important outcomes of treatment which can potentially be extended to screening. Also, the model parameters consider many assumptions and the model uses epidemiological data from a US health survey as opposed to Canadian sources. In addition the study accounts for only

genotype 1 hepatitis C infection, which is only a subset of the population of interest for the CTFPHC guideline on screening for HCV. Therefore, we rated down by 2 points for indirectness.

5. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (55 fewer per 1,000). The entire confidence interval (54 fewer to 56 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. The optimal information size was met. Therefore, we did not rate down for imprecision.
6. Although we included only 1 modeling study, our systematic review of the literature identified several modeling studies looking at the outcomes of interest, which used data sources from different countries some with more favorable results than others. We believe these studies are representative of the research that is readily available, so, therefore we did not rate down for publication bias (other considerations)
7. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (55 fewer per 1,000). The entire confidence interval (55 fewer to 56 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with hepatic decompensation to recommend treating with DAA. The optimal information size was met. Therefore, we did not rate down for imprecision.
8. There were fewer cases of hepatic decompensation when treating with DAA as compared with PR (37 fewer per 1,000). The entire confidence interval (35 fewer to 38 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with hepatic decompensation to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatic decompensation compared to treating with PR. The optimal information size was met. Therefore we did not rate down for imprecision.
9. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (22 fewer per 1,000). The entire confidence interval (21 fewer to 23) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
10. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (23 fewer per 1,000). The confidence interval (23 fewer to 24 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with hepatocellular carcinoma to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. The optimal information size was met. Therefore, we did not rate downgrade for imprecision.
11. There were fewer cases of hepatocellular carcinoma when treating with DAA as compared with PR (21 fewer per 1,000). The entire confidence interval (20 fewer to 22 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. The optimal information size was met. Therefore, we did not rate down for imprecision.
12. There were fewer cases of hepatocellular carcinoma when treating individuals with stage 4 fibrosis with DAA as compared with PR (3 fewer per 1,000). The entire confidence interval (1 fewer to 5 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person developed hepatocellular carcinoma compared to treating with PR. However, the optimal information size was not met. Therefore, we rated down for imprecision.
13. There were individuals who needed liver transplantation when treating with DAA as compared with PR (5 fewer per 1,000). The entire confidence interval (5 fewer to 5 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needs liver transplantation compared to treating with PR. The optimal information size was met. Therefore, we did not rate down for imprecision.
14. There were fewer individuals who needed liver transplantation when treating with DAA as compared with PR (4 fewer per 1,000). The entire confidence interval (4 fewer to 5 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needs liver transplantation compared to treating with PR. The optimal information size was met. Therefore, we did not rate down for imprecision.

15. There were fewer individuals who needed liver transplantation when treating with DAA as compared with PR (4 fewer per 1,000). The entire confidence interval (4 fewer to 5 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needs liver transplantation compared to treating with PR. The optimal information size was not met. Therefore, we rated down for imprecision.
16. There were fewer individuals who needed liver transplantation when treating with DAA as compared with PR (3 fewer per 1,000). The entire confidence interval (2 fewer to 4 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person needs liver transplantation compared to treating with PR. The optimal information size was met. Therefore, we did not rate down for imprecision.
17. There were fewer individuals who died of hepatic complications when treated with DAA as compared with PR (73 fewer per 1,000). The entire confidence interval (71 fewer to 74 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
18. There were fewer individuals who died of hepatic complications when treated with DAA as compared with PR (73 fewer per 1,000). The entire confidence interval (72 fewer to 75 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
19. There were fewer individuals who died of hepatic complications when treated with DAA as compared with PR (71 fewer per 1,000). The entire confidence interval (70 fewer to 72 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.
20. There were fewer individuals who died of hepatic complications when treated with DAA as compared with PR (37 fewer per 1,000). The entire confidence interval (34 fewer to 40 fewer) is to the left of the clinical decision threshold of up to 0 more cases per 1,000 treated, which was established by the CTFPHC as the maximum acceptable number of individuals with this outcome to recommend treating with DAA. In other words, the CTFPHC would recommend against treating with DAA if even 1 more person died due to hepatic complications compared to treating with PR. In addition, the optimal information size was met. Therefore, we did not rate down for imprecision.

Appendix H

Treatment Outcomes and Definitions

Outcome	Definition
Anemia	*Definition in protocol:* feeling weak and tired, because people have low levels of red blood cells. Red blood cells carry oxygen to the body To include # of cases of the following: - In non-pregnant adult females, hemoglobin levels <120 g/l - In adult males, hemoglobin levels <130 g/l - If study does not separate out hemoglobin level definitions by gender, then suggest to include cases with hemoglobin levels <120 g/l
Cirrhosis	*Definition in protocol:* developing cirrhosis (permanent liver scarring) To include # of cases identified as having cirrhosis (all levels)
Flu-like symptoms	*Definition in protocol:* experiencing flu-like symptoms To include # of cases identified as having the following: - Influenza-like or flu-like symptoms, or - Fever (including low-grade)
Hepatic decompensation	*Definition in protocol:* developing liver damage that is so severe that people will not survive without a liver transplant To include # of cases identified as having hepatic decompensation or decompensated liver disease, or any one, or combination, of the following outcomes: - ascites - hepatic encephalopathy - acute variceal bleeding or variceal hemorrhage
Hepatocellular carcinoma	*Definition in protocol:* developing liver cancer To include # of cases identified as having hepatocellular carcinoma or liver cancer
Histological improvements	*Definition in protocol:* improvement in the health of the liver To include # of cases showing improvements in either grade or stage of liver disease using any of the following scoring systems: - Knodell - Ishak - Batts and Ludwig - METAVIR - IASL
Mortality (all cause)	*Definition in protocol:* dying from causes other than liver disease To include all reported cases of deaths (for any reason) except those specifically identified as being due to liver disease ***NOTE:*** normally all-cause mortality should include deaths due to liver disease…but in this case it was excluded
Mortality	*Definition in protocol:* dying from liver disease

(hepatic)	To include all reported cases of deaths specifically identified as being due to liver disease
Need for liver transplantation	*Definition in protocol:* needing a liver transplant To include # of cases identified as needing/requiring a liver transplant (or having undergone a liver transplant) post-treatment.
Neutropenia	*Definition in protocol:* being more vulnerable to infections because people have low levels of neutrophils in their body. Neutrophils are cells that help to fight infections To include # of cases with ANC counts <1500 cells per microliter of blood
Psychological adverse events	*Definition in protocol:* experiencing unpleasant psychological side effects (e.g. depression) For psychological adverse events, include # of cases identified as having the following: affect liability, aggression, anxiety, completed suicide, confusion, confusional state, depressed mood, depression, disturbance in attention, drug dependence, homicidal ideation, insomnia, intentional self-injury, irritability, major depression, memory impairment, mood altered, mood swings, panic attack, paranoia, psychiatric decompensation, suicidal ideation, suicide attempt
Quality of life	*Definition in protocol:* quality of life To include the following scales measuring quality of life or health-related quality of life: - Short-form 36 questionnaire - EQ-5D quality of life questionnaire
Rash	*Definition in protocol:* developing skin rashes To only include # of cases specifically identified as having a "rash" (i.e. exclude itchiness/itchy, etc.)
Reduced HCV transmission	*Definition in protocol:* being less likely to infect another person with Hepatitis C
Sustained virological response	*Definition in protocol:* getting successfully treated for the virus so that the virus is cleared from the body. Although this isn't a cure, people are less likely to develop liver cancer or die when the virus has been cleared from their body To include # of cases meeting SVR at 24 weeks (or with HCV RNA levels using a sensitive assay that has a lower limit of detection of 50 IU/ml or less, ideally by real-time PCR) - SVR at 12 and 72 weeks post-treatment will be collected as well and analyzed separately
Withdrawals due to adverse events	*Definition in protocol:* experiencing unpleasant side effects that lead people to stop taking their medication. This can reduce the chance that the treatment will work To include # of cases that withdrew due to unpleasant side effects (whether or not the symptoms could be directly linked to the treatment)

Appendix I

Clinical Decision Thresholds and Optimal Information Size

Clinical Decision Thresholds

The following are clinical decision thresholds (i.e. threshold for which a clinical decision is made between recommending or not recommending treatment) we used for various outcomes.

These recommendations are based on clinical expert advice and from the results of the Patient Preferences Survey, where patients ranked and provided input on which outcomes were more important in their decision to undergo hepatitis C treatment versus others. In general, treatment benefits (except all-cause mortality) were ranked as critical by the patients whereas treatment harms were ranked as important. Some harms (i.e. anemia, neutropenia, psychological adverse events and withdrawal due to adverse events) were ranked more importantly than others (i.e. rash and flu-like symptoms).

What is a clinical decision threshold (CDT) between recommending and not recommending DAA-based treatment versus PR for the following outcomes?

1) Sustained virological response (SVR12, SVR24 or SVR72)

   Suggest NOT recommending more expensive DAA-based regimens if the lower limit of the confidence interval of the absolute effect includes 50 (in other words, 50 less people per 1000 treated will achieve SVR in the DAA-based regimen group versus PR group). *This equates to at least a 5% reduction in SVR in the DAA-based group vs. PR group.*

   Rationale: The slightly lower SVR rate would be offset by the improved tolerability of the DAA-regimen.

2) Mortality (all-cause), mortality (hepatic), hepatocellular carcinoma, hepatic decompensation & need for liver transplantation

   Suggest NOT recommending more expensive DAA-based regimens:

a) if no significant improvement in rates of SVR were observed between the DAA group and PR group, OR
b) if the upper limit of the confidence interval of the absolute effect includes 1 (~~,~~in other words, 1 more person per 1000 treated will die from all causes or liver-related disease, develop hepatocellular carcinoma, hepatic decompensation, or will need liver transplantation in the DAA-based regimen group versus PR group).

   Rationale: It would be hard to recommend "better-tolerated" therapy at any expense of hard clinical endpoints such as these.

3) Anemia, neutropenia, psychological adverse events, withdrawal due to adverse events

   Suggest NOT recommending DAA-based regimens if the upper limit of the confidence interval of the absolute effect includes 50 (in other words, 50 more people per 1000 treated will experience/develop anemia, neutropenia, psychological adverse events or will withdraw from the study/treatment due to adverse events in the DAA-based regimen group versus PR group). *This equates to at least a 5% increase in the aforementioned outcomes in the DAA-based group vs. PR group.*

Rationale: Patients would generally accept a higher rate of adverse events if it resulted in a higher rate of SVR (and likely a reduction in clinical important outcomes such as those indicated in #2 above).

4) Rash & flu-like symptoms

Suggest NOT recommending DAA-based regimens if the upper limit of the confidence interval of the absolute effect includes 100 (in other words, 100 more people per 1000 treated will experience/develop rash or flu-like symptoms in the DAA-based regimen group versus PR group). *This equates to at least a 10% increase in the aforementioned outcomes in the DAA-based group vs. PR group.*

Rationale: Patients would generally accept a higher rate of adverse events if it resulted in a higher rate of SVR (and likely a reduction in clinical important outcomes such as those indicated in #2 above).

Optimal Information Size (OIS)[26] assessments

RCT's with PR control	The number of patients required for an adequately powered individual trial: minimum sample size per group (treatment & control assessed separately)	OIS met?
All DAA's		
1.1 SVR12	84	YES
1.2 SVR24	81	YES
1.3 SVR72	70	YES
1.4 Mortality (all cause)	3920 (Note: this value is NOT reliable due to small # of events)	NO
2.1 Anemia	4,495	NO
2.2 Flu-like symptoms	100,653	NO
2.3 Neutropenia	34,446	NO
2.4 Psychological adverse events	2,495	YES
2.5 Rash	2,750,211	NO
2.6 Withdrawal due to adverse events	326	YES
SIM+PR		
4.1 SVR12	58	YES
4.2 SVR12 - F0-F2	40	YES
4.3 SVR12 - F3-F4	37	YES
4.4 SVR24	55	YES
4.5 SVR24 F0-F2	84	NO
4.6 SVR24 F3-F4	2,083	NO
4.7 SVR72	70	YES
4.8 Anemia	1,207	NO
4.9 Flu-like symptoms	19,128	NO
4.10 Neutropenia	6,112	NO
4.11 Psychological adverse events	3,720	NO
4.12 Rash	2,947,250	NO
4. 13 Withdrawal due to adverse events	9,581	NO
SOF+PR		
5.1 SVR12	27	NO
5.2 SVR24	35	NO
5.3 Anemia	591	NO
5.4 Flu-like symptoms	85	NO
5.5 Neutropenia	1,066	NO
5.6 Psychological adverse events	1,394	NO
5.7 Rash	121	NO
5.8 Withdrawal due to adverse events	151	NO
SOF+RBV		
6.1 SVR12	138,937	NO
6.2 SVR24	17,946	NO
6.3 Anemia	1,279	NO
6.4 Flu-like symptoms	61	YES

6.5 Neutropenia	59 (Note: this value is NOT reliable due to no events reported in the DAA group)	YES
6.6 Psychological adverse events	426	YES
6.7 Rash	239	YES
6.8 Withdrawal due to adverse events	83	YES
Modelling studies		
All DAA's		
1.5 Mortality (hepatic)	320	YES
1.6 Mortality (hepatic) - F0-F1	300	YES
1.12 Mortality (hepatic) - F2-F3	338	YES
1.13 Mortality (hepatic) - F4	2,812	YES
1.14 Hepatocellular carcinoma	1,860	YES
1.15 Hepatocellular carcinoma - F0-F1	1,689	YES
1.16Hepatocellular carcinoma - F2-F3	2,037	YES
1.18 Hepatocellular carcinoma - F4	Infinity	NO
1.19 Hepatic decompensation	311	YES
1.20 Hepatic decompensation - F0-F1	311	YES
1.21 Hepatic decompensation - F2-F3	318	YES
1.22 Hepatic decompensation - F4	1,630	YES
1.23 Need for liver transplantation	4,880	YES
1.24 LT - F0-F1	7,813	YES
1.25 LT - F2-F3	4,880	YES
1.26 LT - F4	31,144	YES
SOF + LDV		
3.13 Mortality (hepatic)	193	YES
3.14 Mortality (hepatic) - F0-F1	183	YES
3.15Mortality (hepatic) - F2-F3	212	YES
3.16Mortality (hepatic) - F4	1,186	YES
3.5 Hepatocellular carcinoma	1,185	YES
3.6 Hepatocellular carcinoma - F0-F1	1,098	YES
3.7 Hepatocellular carcinoma - F2-F3	1,448	YES
3.8 Hepatocellular carcinoma - F4	258,851	NO
3.1 Hepatic decompensation	178	YES
3.2 Hepatic decompensation - F0-F1	178	YES
3.3 Hepatic decompensation - F2-F3	183	YES
3.4 Hepatic decompensation - F4	595	YES
3.9 Need for liver transplantation	2,812	YES
3.10 LT - F0-F1	3,908	YES
3.11 LT - F2-F3	2,812	YES
3.12 LT - F4	12,983	YES
OMB/PAR/RIT + DAS ± RBV		
7.13 Mortality (hepatic)	207	YES
7.14 Mortality (hepatic) - F0-F2	196	YES

7.15 Mortality (hepatic) - F2-F3	220	YES
7.16 Mortality (hepatic) - F4	1,405	YES
7.5 Hepatocellular carcinoma	1,185	YES
7.6 Hepatocellular carcinoma - F0-F1	1,098	YES
7.7 Hepatocellular carcinoma - F2-F3	1,448	YES
7.8 Hepatocellular carcinoma - F4	114,296	NO
7.1 Hepatic decompensation	196	YES
7.2 Hepatic decompensation - F0-F1	196	YES
7.3 Hepatic decompensation - F2-F3	201	YES
7.4 Hepatic decompensation - F4	798	YES
7.9 Need for liver transplantation	2,812	YES
7.10 LT - F0-F1	3,908	YES
7.11 LT - F2-F3	2,812	YES
7.12 LT - F4	12,983	YES

Appendix J

Summary of key findings from RCTs for benefits and harms of treatment with DAA versus PR alone

Outcome	Comparator	Absolute Risk Difference (Range)	Risk Ratio (95% CI)	NNT*
SVR 12	All DAA[a]	181 more per 1,000 (137 to 230)	1.29 (1.22, 1.37)	6
	Simeprevir+PR [d]	230 more per 1,000 (176 to 291)	1.38 (1.29, 1.48)	4
	Simeprevir+PR [d] (F0-F2[c])	287 more per 1,000 (182 to 409)	1.52 (1.33, 1.74)	3
	Simeprevir+PR [d] (F3-F4 [c])	329 more per 1,000 (134 to 599)	1.91 (1.37, 2.66)	3
	Sofosbuvir+PR [e]	329 more per 1,000 (69 to 687)	1.57 (1.12, 2.19)	3
	Sofosbuvir+ribavirin (interferon-free) [f]	No difference	1.01 (0.89, 1.14)	-
SVR 24	All DAA[a]	190 more per 1,000 (141 to 239)	1.31 (1.23, 1.39)	5
	Simeprevir+PR [d]	238 more per 1000 (184 to 303)	1.40 (1.31, 1.51)	4
	Simeprevir+PR [d] (F0-F2 [c])	186 more per 1,000 (51 to 354)	1.29 (1.08, 1.55)	5
	Sofosbuvir+PR [e]	294 more per 1,000 (46 to 646)	1.57 (1.08, 2.12)	3
	Sofosbuvir+ribavirin [f]	No difference	1.02 (0.90, 1.98)	-
	Simeprevir+PR [d] (F3-F4 [c])	No difference	0.94 (0.57, 1.57)	-
SVR 72	All DAA [d]	215 more per 1,000 (156 to 281)	1.36 (1.26, 1.47)	5
	Simeprevir+PR [d]	215 more per 1,000 (156 to 281)	1.36 (1.26, 1.47)	5
All-cause Mortality	All DAA[b]	No difference	2.14 (0.23, 20.01)	-
Quality of Life	All DAA[b]	No significant difference based on narrative review of quantitative data	N/A	-
Anemia	All DAA[a]	42 fewer per 1,000 (10 to 69)	0.83 (0.72, 0.96)	24
	Simeprevir+PR [d]	No difference	0.85 (0.73, 1.00)	-
	Sofosbuvir+PR [e]	No difference	0.74 (0.35, 1.57)	-
	Sofosbuvir+ribavirin [f]	No difference	0.71 (0.42, 1.22)	-
Flu-like Symptoms	Sofosbuvir+ribavirin [f]	154 fewer per 1,000 (121 to 168)	0.15 (0.07, 0.33)	6
	All DAA[a]	No difference	0.83 (0.70, 1.00)	-
	Simeprevir+PR[d]	No difference	0.99 (0.82, 1.20)	-
	Sofosbuvir+PR [e]	No difference	3.01 (0.76, 11.98)	-
Neutropenia	Sofosbuvir+ribavirin [f]	121 fewer per 1,000 (0 to 0.25)	0.02 (0.00, 0.25)	8
	All DAA[a]	No difference	0.90 (0.74, 1.10)	-
	Simeprevir+PR[d]	No difference	0.99 (0.82, 1.20)	-
	Sofosbuvir+PR[e]	No difference	1.26 (0.53, 2.99)	-
Psychological Adverse Events	All DAA[a]	30 fewer per 1,000 (22 to 37)	0.68 (0.61, 0.77)	33
	Simeprevir+PR [d]	21 fewer per 1,000 (8 to 31)	0.80 (0.70, 0.92)	48
	Sofosbuvir+ribavirin [f]	46 fewer per 1,000 (36 to 53)	0.44 (0.35, 0.56)	22
	Sofosbuvir+PR [e]	No difference	0.74 (0.48, 1.13)	-
Rash	Sofosbuvir+ribavirin [f]	87 fewer per 1,000 (32 to 120)	0.51 (0.32, 0.82)	11
	All DAA[a]	No difference	1.08 (0.88, 1.33)	-
	Simeprevir+PR [d]	No difference	1.00 (0.85, 1.19)	-
	Sofosbuvir+PR [e]	No difference	1.98 (0.77, 5.14)	-
Withdrawal due to Adverse Events	All DAA[a]	35 fewer per 1,000 (23 to 41)	0.30 (0.17, 0.53)	29
	Sofosbuvir+ribavirin [f]	107 fewer per 1,000 (81 to 116)	0.10 (0.03, 0.32)	9
	Simeprevir+PR [d]	No difference	0.73 (0.35, 1.53)	-
	Sofosbuvir+PR [e]	No difference	0.14 (0.01, 1.45)	-

* Number Needed to Treat represents the number of people who need to receive DAA-based regimens rather than PR for one additional person to either incur a benefit (e.g. SVR12) or avoid a harmful event (e.g. psychological adverse event).

[a] Trials Included the following DAA-based regimens in HCV genotypes 1-3 subjects: simeprevir+PR, sofosbuvir+PR and sofosbuvir+ribavirin (interferon-free); [b] Trials Included the following DAA-based regimens in HCV genotypes 1-3 subjects:

simeprevir+PR and sofosbuvir+ribavirin (interferon-free); [c] Metavir fibrosis score; [d] All trials were on simeprevir+PR in HCV genotype 1 subjects; [e] Data was from one RCT in HCV genotype 1 subjects; [f] Data was from one RCT in HCV genotypes 2 and 3 subjects.

Summary of key findings from a modelling study on the benefits of treatment with DAA versus PR alone in all subjects and by Metavir fibrosis score

Outcome	**Fibrosis Score**	**All DAA[b]**	**Sofosbuvir+Ledipasvir** (interferon-free)	**Ombitasvir/Paritaprevir/ Ritonavir + Dasabuvir (± Ribavirin)** (interferon-free)
Hepatic Mortality	All	60 fewer per 1,000 (59 fewer to 62 fewer) RR 0.45 (0.44, 0.46) NNT 17	75 fewer per 1,000 (74 fewer to 75 fewer) RR 0.32 (0.32, 0.33) NNT 13	73 fewer per 1,000 (71 fewer to 74 fewer) RR 0.34 (0.33, 0.35) NNT 14
	F0-F1	62 fewer per 1,000 (61 fewer to 62 fewer) RR 0.44 (0.44, 0.45) NNT 16	76 fewer per 1,000 (75 fewer to 77 fewer) RR 0.32 (0.31, 0.33) NNT 13	73 fewer per 1,000 (72 fewer to 75 fewer) RR 0.34 (0.33, 0.35) NNT 14
	F2-F3	60 fewer per 1,000 (59 fewer to 61 fewer) RR 0.48 (0.47, 0.49) NNT 17	73 fewer per 1,000 (72 fewer to 73 fewer) RR 0.36 (0.36, 0.37) NNT 14	71 fewer per 1,000 (70 fewer to 72 fewer) RR 0.38 (0.37, 0.39) NNT 14
	F4	26 fewer per 1,000 (25 fewer to 28 fewer) RR 0.83 (0.82, 0.84) NNT 38	40 fewer per 1,000(37 fewer to 41 fewer) RR 0.74 (0.73, 0.76) NNT 25	37 fewer per 1,000 (71 fewer to 74 fewer) RR 0.76 (0.74, 0.78) NNT 27
Hepatocellular Carcinoma	All	18 fewer per 1,000 (17 fewer to 19 fewer) RR 0.63 (0.61, 0.65) NNT 56	22 fewer per 1,000 (21 fewer to 23 fewer) RR 0.55 (0.53, 0.57) NNT 45	22 fewer per 1,000 (21 fewer to 23 fewer) RR 0.55 (0.53, 0.58) NNT 45
	F0-F1	20 fewer per 1,000 (19 fewer to 20 fewer) RR 0.61 (0.60, 0.62) NNT 50	24 fewer per 1,000 (23 fewer to 24 fewer) RR 0.53 (0.52, 0.54) NNT 42	23 fewer per 1,000 (23 fewer to 24 fewer) RR 0.54 (0.52, 0.55) NNT 43
	F2-F3	18 fewer per 1,000 (17 fewer to 19 fewer) RR 0.67 (0.65, 0.68) NNT 56	21 fewer per 1,000 (20 fewer to 22 fewer) RR 0.60 (0.59, 0.62) NNT 48	21 fewer per 1,000 (20 fewer to 22 fewer) RR 0.60 (0.59, 0.62) NNT 48
	F4	No difference (1 fewer to 1 more) RR 1.00 (0.98, 1.02) NNT	No difference (0 fewer to 4 fewer) RR 0.97 (0.95, 1.00) NNT	3 fewer per 1,000 (1 fewer to 5 fewer) RR 0.96 (0.93, 0.99) NNT 333
Hepatic Decompensation	All	46 fewer per 1,000 (46 fewer to 47 fewer) RR 0.31 (0.30, 0.32) NNT 22	57 fewer per 1,000 (56 fewer to 58 fewer) RR 0.15 (0.14, 0.16) NNT 18	55 fewer per 1,000(54 fewer to 56 fewer) RR 0.18 (0.17, 0.19) NNT 18
	F0-F1	46 fewer per 1,000 (46 fewer to 47 fewer) RR 0.31 (0.30, 0.32) NNT 22	57 fewer per 1,000 (57 fewer to 58 fewer) RR 0.15 (0.14, 0.15) NNT 18	55 fewer per 1,000 (55 fewer to 56 fewer) RR 0.18 (0.17, 0.18) NNT 18
	F2-F3	46 fewer per 1,000 (46 fewer to 47 fewer) RR 0.32 (0.31, 0.33) NNT 22	57 fewer per 1,000 (56 fewer to 57 fewer) RR 0.16 (0.16, 0.17) NNT 18	55 fewer per 1,000 (54 fewer to 56 fewer) RR 0.19 (0.18, 0.20) NNT 18
	F4	27 fewer per 1,000 (25 fewer to 28 fewer) RR 0.70 (0.69, 0.72)	41 fewer per 1,000 (39 fewer to 42 fewer) RR 0.54 (0.53, 0.56)	37 fewer per 1,000 (35 fewer to 38 fewer) RR 0.59 (0.57, 0.61)

		NNT 37	NNT 24	NNT 27
Need for Liver Transplantation	All	4 fewer per 1,000 (4 fewer to 5 fewer) RR 0.39 (0.35, 0.42) NNT 250	5 fewer per 1,000 (5 fewer to 5 fewer) RR 0.25 (0.22, 0.29) NNT 200	5 fewer per 1,000 (5 fewer to 5 fewer) RR 0.26 (0.23, 0.31) NNT 200
	F0-F1	4 fewer per 1,000 (3 fewer to 4 fewer) RR 0.43 (0.40, 0.45) NNT 250	5 fewer per 1,000 (4 fewer to 5 fewer) RR 0.29 (0.27, 0.32) NNT 200	4 fewer per 1,000 (4 fewer to 5 fewer) RR 0.30 (0.27, 0.34) NNT 250
	F2-F3	4 fewer per 1,000 (4 fewer to 4 fewer) RR 0.44 (0.41, 0.47) NNT 250	5 fewer per 1,000 (4 fewer to 5 fewer) RR 0.31 (0.29, 0.34) NNT 200	4 fewer per 1,000 (4 fewer to 5 fewer) RR 0.33 (0.29, 0.36) NNT 250
	F4	2 fewer per 1,000 (1 fewer to 2 fewer) RR 0.82 (0.76, 0.88) NNT 500	3 fewer per 1,000 (2 fewer to 3 fewer) RR 0.68 (0.62, 0.74) NNT 333	3 fewer per 1,000 (2 fewer to 4 fewer) RR 0.66 (0.59, 0.73) NNT 333

[a] Data was modelled on HCV genotype 1 subjects; [b] the following regimens were included in the model: sofosbuvir+PR, sofosbuvir+ribavirin, simeprevir+sofosbuvir, sofosbuvir+ledipasvir and ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin.

Appendix K

Fibrosis Scores at Baseline

Study	Range of fibrosis/cirrhosis at baseline by treatment arm %	% Population that does not have cirrhosis
Fried 2013[28]	F0=9-16%; F1=33-46%; F2=32-35%, F3=9-23% Excluded patients with cirrhosis	100%
Hayashi 2014[29]	F0=0-7%; F1=68-75%; F2=20-21%; F3=4-5% Excluded patients with cirrhosis	100%
Jacobson 2014[30]	F0-F1= 38-45%; F2=25-31%; F3=17-18%; F4= 12-13%	88-87%
Lawitz 2013-1[36]	Arm 1 - 50 participants with cirrhosis (20%) Control - 50 participants with cirrhosis (21%)	79-80%
Lawitz 2013-2[37]	No or minimal 12-25%; portal fibrosis 73-81%; bridging fibrosis 2-8% Excluded patients with cirrhosis	100%
Manns 2014[31]	F0-F1=45-52%; F2=26-31%; F3=13-15; F4=7-11%	89-93%
NCT01725529 2015[32]	Not provided	n/a

Chahal modelling study[38] provided for comparison	F0=17%; F1=35%; F2=22%; F3=14% F4=12%	88%

Appendix L

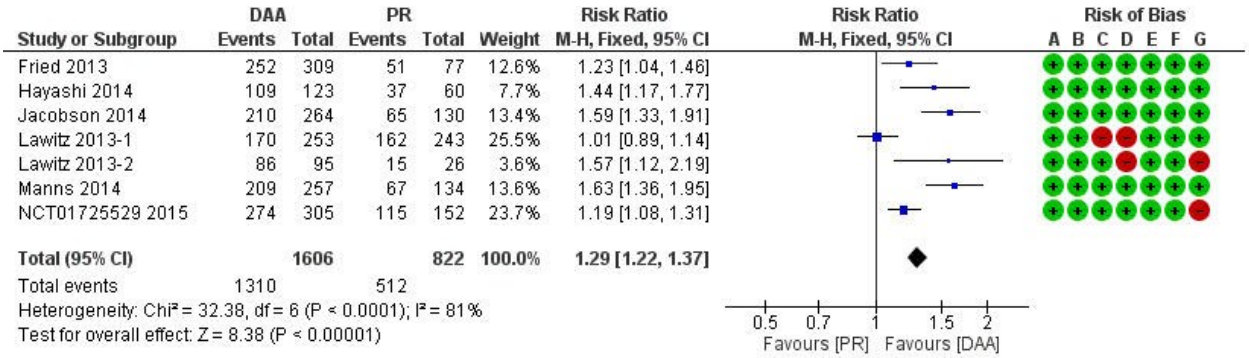
Data analysis, forest plots and Cochrane risk of bias[21] assessments by outcome

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

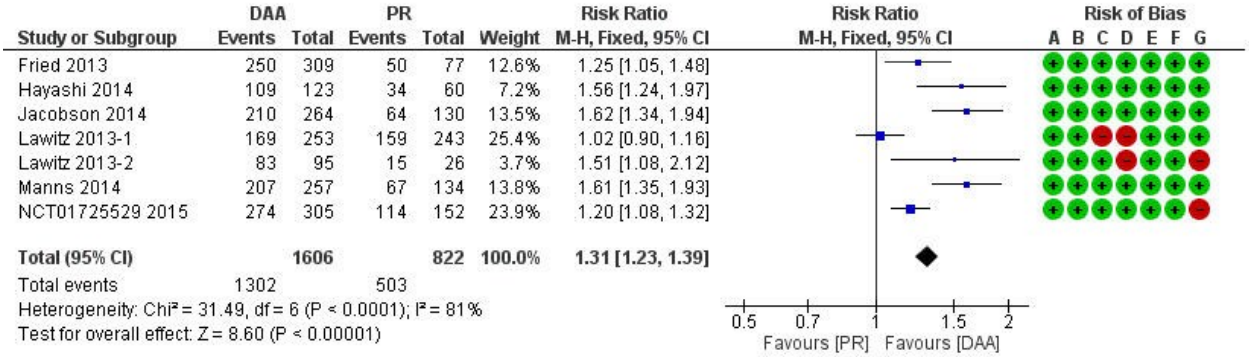
Q1.1 Sustained Virological Respose (SVR)

Q1.1a DAA versus PR

SVR12



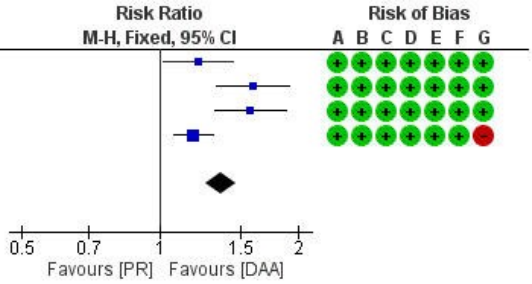
SVR24



SVR72

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fried 2013	243	309	50	77	19.7%	1.21 [1.02, 1.44]
Jacobson 2014	207	264	64	130	21.1%	1.59 [1.32, 1.92]
Manns 2014	202	257	67	134	21.7%	1.57 [1.31, 1.88]
NCT01725529 2015	271	305	114	152	37.5%	1.18 [1.07, 1.31]
Total (95% CI)		**1135**		**493**	**100.0%**	**1.36 [1.26, 1.47]**
Total events	923		295			

Heterogeneity: Chi² = 14.26, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 7.88 (P < 0.00001)

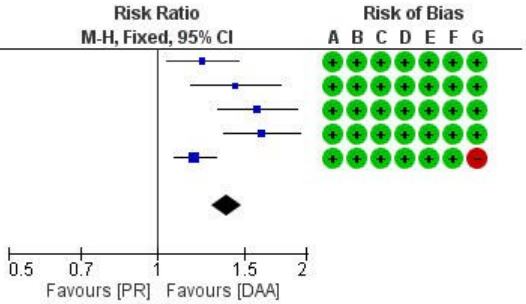


Q1.1b Simeprevir+PR versus PR

SVR 12

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fried 2013	252	309	51	77	17.7%	1.23 [1.04, 1.46]
Hayashi 2014	109	123	37	60	10.8%	1.44 [1.17, 1.77]
Jacobson 2014	210	264	65	130	18.9%	1.59 [1.33, 1.91]
Manns 2014	209	257	67	134	19.1%	1.63 [1.36, 1.95]
NCT01725529 2015	274	305	115	152	33.4%	1.19 [1.08, 1.31]
Total (95% CI)		**1258**		**553**	**100.0%**	**1.38 [1.29, 1.48]**
Total events	1054		335			

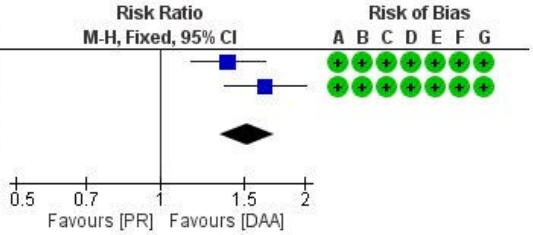
Heterogeneity: Chi² = 16.70, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 8.98 (P < 0.00001)



SVR 12 – F0-F2

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jacobson 2014	152	183	54	90	51.5%	1.38 [1.16, 1.66]
Manns 2014	165	195	52	102	48.5%	1.66 [1.36, 2.03]
Total (95% CI)		**378**		**192**	**100.0%**	**1.52 [1.33, 1.74]**
Total events	317		106			

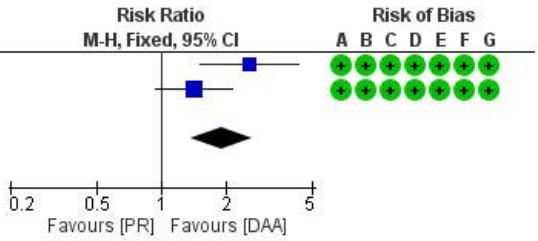
Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 6.07 (P < 0.00001)



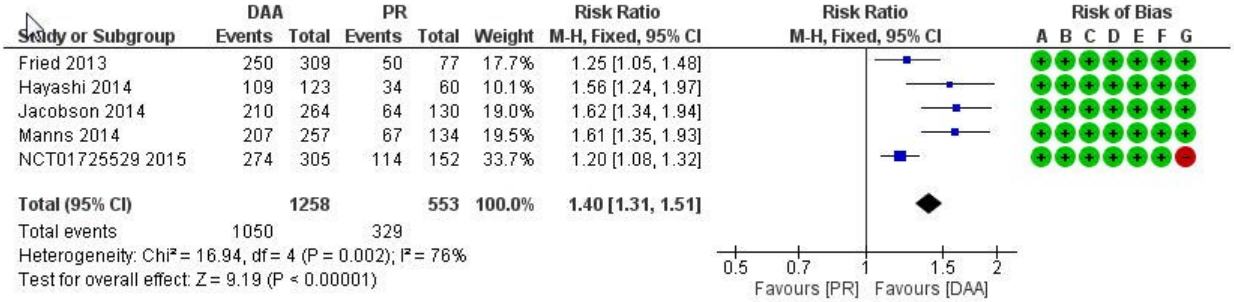
SVR 12 – F3-F4

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jacobson 2014	54	77	11	40	43.6%	2.55 [1.51, 4.31]
Manns 2014	35	53	15	32	56.4%	1.41 [0.93, 2.14]
Total (95% CI)		**130**		**72**	**100.0%**	**1.91 [1.37, 2.66]**
Total events	89		26			

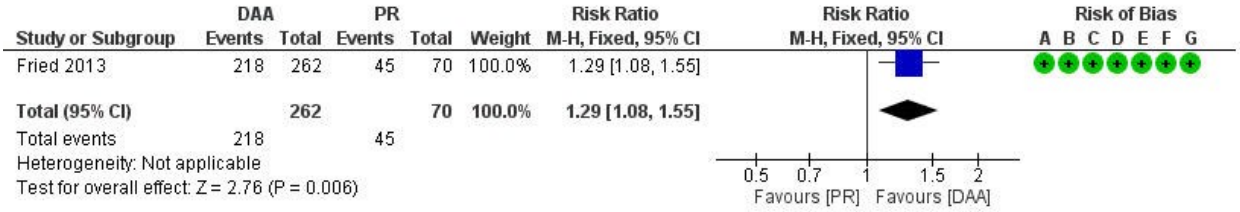
Heterogeneity: Chi² = 3.21, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 3.80 (P = 0.0001)



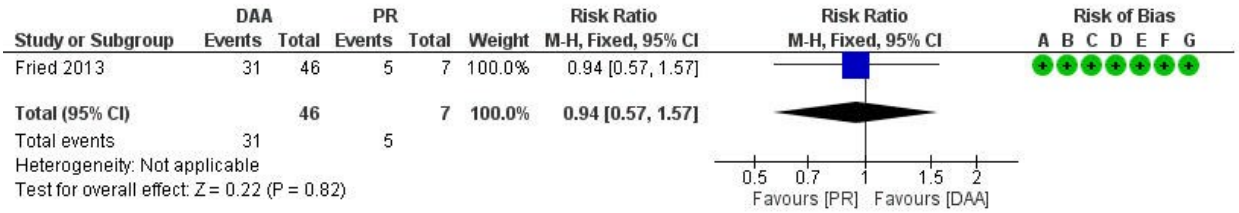
SVR 24



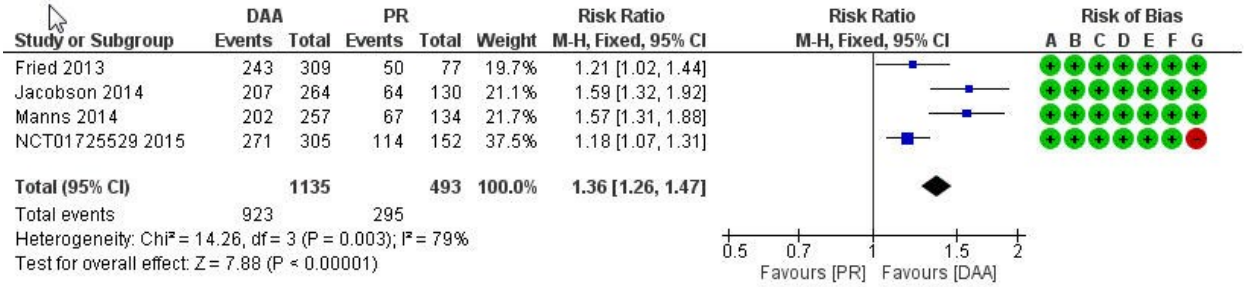
SVR 24 – F0-F2



SVR 24 – F3-F4

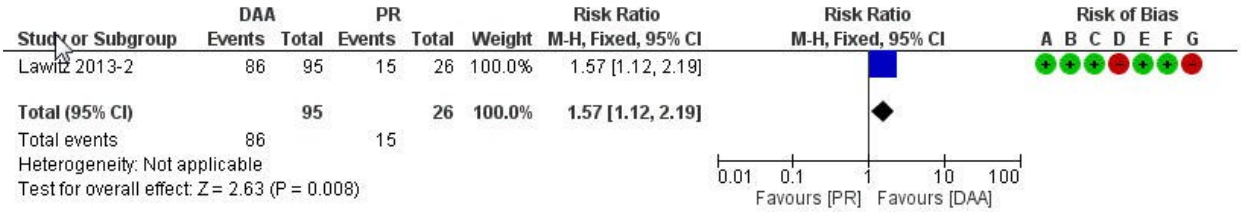


SVR 72

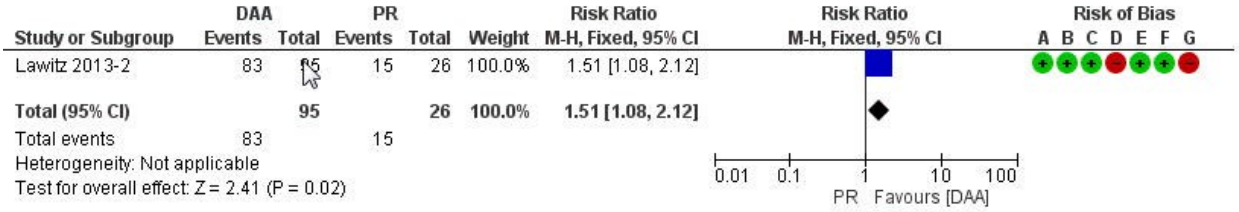


Q1.1c Sofosbuvir+PR versus PR

SVR 12

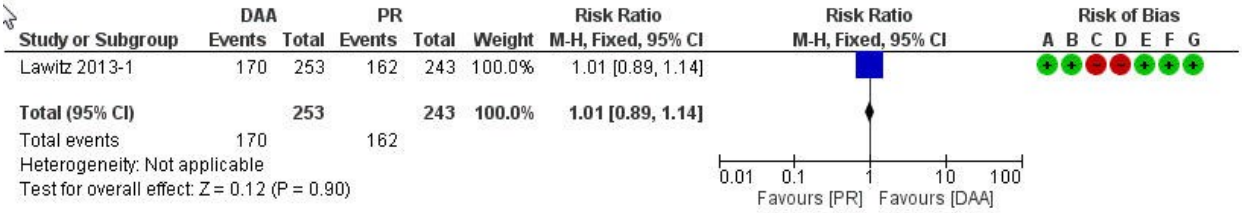


SVR 24

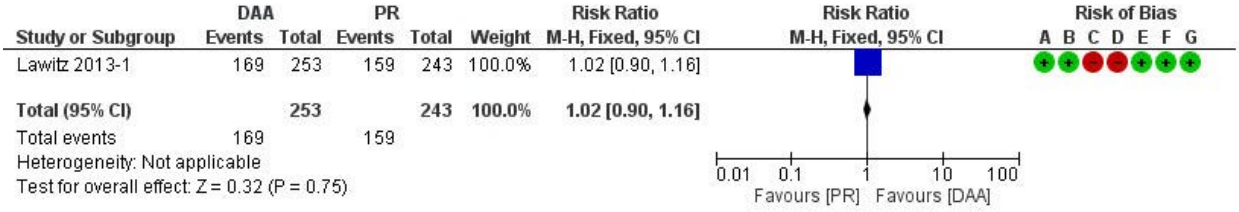


Q1.1d Sofosbuvir+Ribavirin versus PR

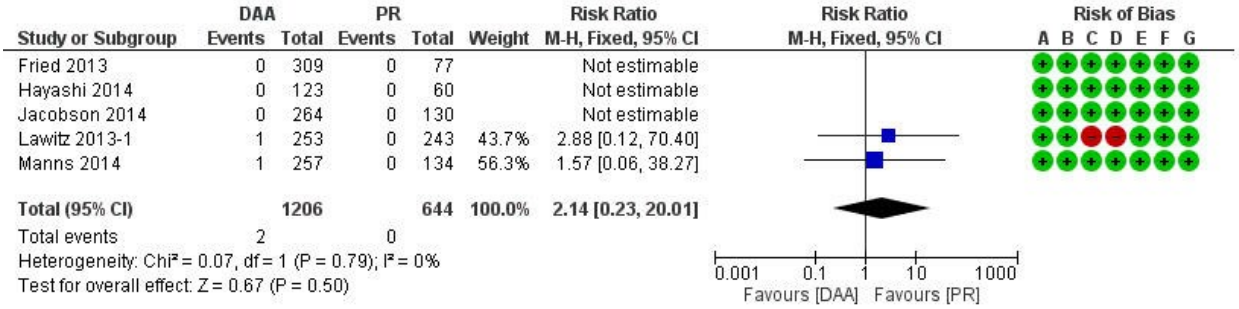
SVR 12



SVR 24



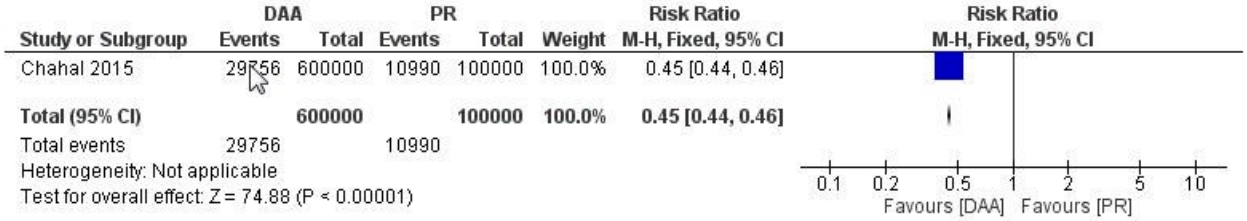
Q1.2 All-Cause Mortality



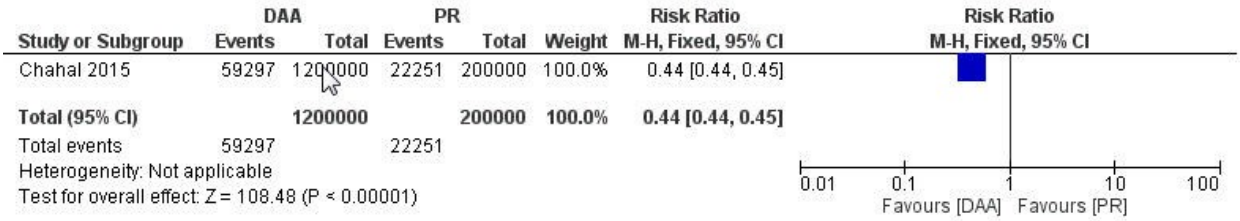
Q1.3 Hepatic Mortality

Q1.3 DAA versus PR

Hepatic Mortality

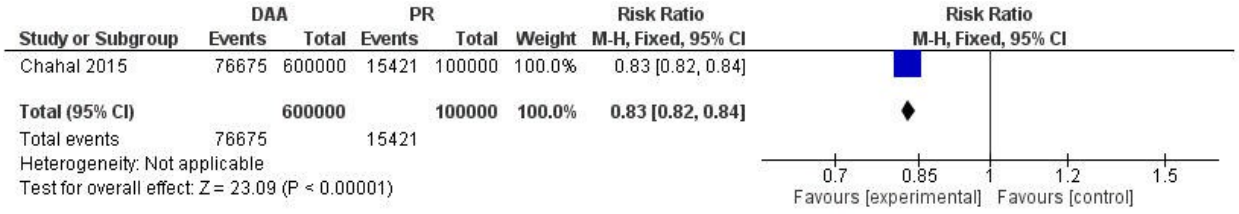


Hepatic Mortality – F0-F1



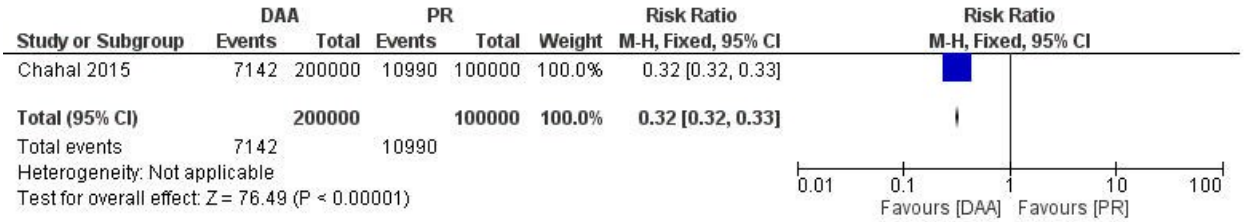
Hepatic Mortality – F2-F3

Hepatic Mortality – F4



Q1.3a Sofosbuvir+Ledipasvir versus PR

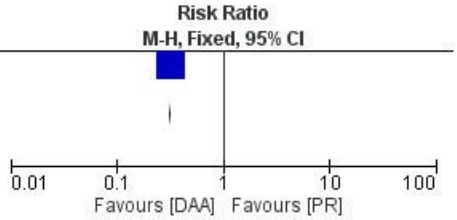
Hepatic Mortality



Hepatic Mortality – F0-F1

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	14188	400000	22251	200000	100.0%	0.32 [0.31, 0.33]
Total (95% CI)		**400000**		**200000**	**100.0%**	**0.32 [0.31, 0.33]**
Total events	14188		22251			

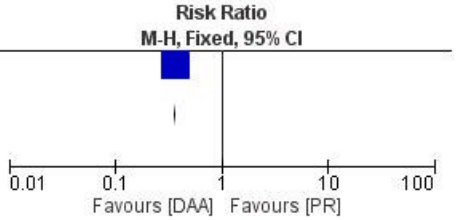
Heterogeneity: Not applicable
Test for overall effect: Z = 110.04 (P < 0.00001)



Hepatic Mortality – F2-F3

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	16687	400000	22963	200000	100.0%	0.36 [0.36, 0.37]
Total (95% CI)		**400000**		**200000**	**100.0%**	**0.36 [0.36, 0.37]**
Total events	16687		22963			

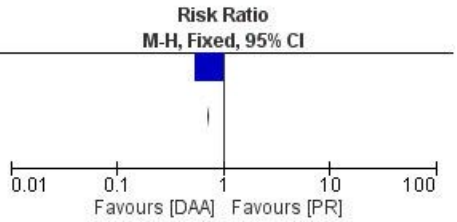
Heterogeneity: Not applicable
Test for overall effect: Z = 103.34 (P < 0.00001)



Hepatic Mortality – F4

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	22610	200000	15241	100000	100.0%	0.74 [0.73, 0.76]
Total (95% CI)		**200000**		**100000**	**100.0%**	**0.74 [0.73, 0.76]**
Total events	22610		15241			

Heterogeneity: Not applicable
Test for overall effect: Z = 30.68 (P < 0.00001)

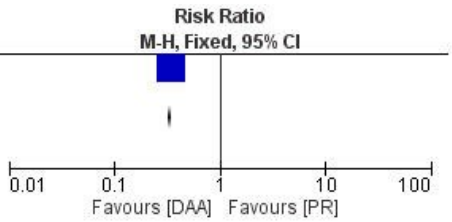


Q1.3b Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir ± Ribavirin (3D±Ribavirin) versus PR

Hepatic Mortality

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	3751	100000	10990	100000	100.0%	0.34 [0.33, 0.35]
Total (95% CI)		**100000**		**100000**	**100.0%**	**0.34 [0.33, 0.35]**
Total events	3751		10990			

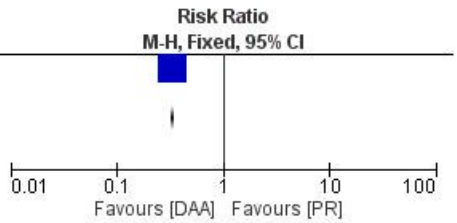
Heterogeneity: Not applicable
Test for overall effect: Z = 58.51 (P < 0.00001)



Hepatic Mortality – F0-F1

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	7490	200000	22251	200000	100.0%	0.34 [0.33, 0.35]
Total (95% CI)		**200000**		**200000**	**100.0%**	**0.34 [0.33, 0.35]**
Total events	7490		22251			

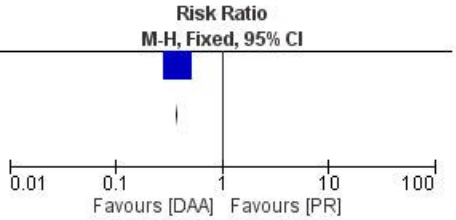
Heterogeneity: Not applicable
Test for overall effect: Z = 83.89 (P < 0.00001)



Hepatic Mortality – F2-F3

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	8668	200000	22963	200000	100.0%	0.38 [0.37, 0.39]
Total (95% CI)		**200000**		**200000**	**100.0%**	**0.38 [0.37, 0.39]**
Total events	8668		22963			

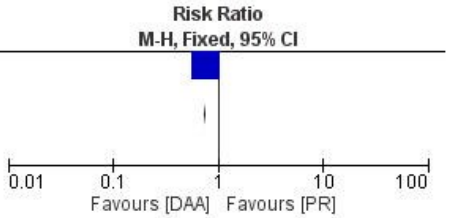
Heterogeneity: Not applicable
Test for overall effect: Z = 79.84 (P < 0.00001)



Hepatic Mortality – F4

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	11595	100000	15241	100000	100.0%	0.76 [0.74, 0.78]
Total (95% CI)		**100000**		**100000**	**100.0%**	**0.76 [0.74, 0.78]**
Total events	11595		15241			

Heterogeneity: Not applicable
Test for overall effect: Z = 23.81 (P < 0.00001)



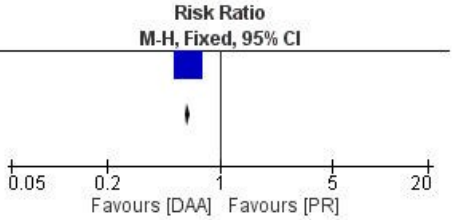
Q1.4 Hepatocellular Carcinoma

Q1.4 DAA versus PR

Hepatocellular Carcinoma

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	18456	600000	4890	100000	100.0%	0.63 [0.61, 0.65]
Total (95% CI)		**600000**		**100000**	**100.0%**	**0.63 [0.61, 0.65]**
Total events	18456		4890			

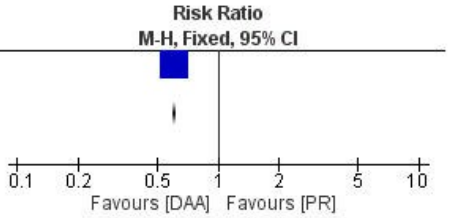
Heterogeneity: Not applicable
Test for overall effect: Z = 29.49 (P < 0.00001)



Hepatocellular Carcinoma – F0-F1

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	36784	1200000	10068	200000	100.0%	0.61 [0.60, 0.62]
Total (95% CI)		**1200000**		**200000**	**100.0%**	**0.61 [0.60, 0.62]**
Total events	36784		10068			

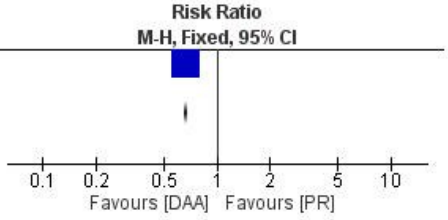
Heterogeneity: Not applicable
Test for overall effect: Z = 45.16 (P < 0.00001)



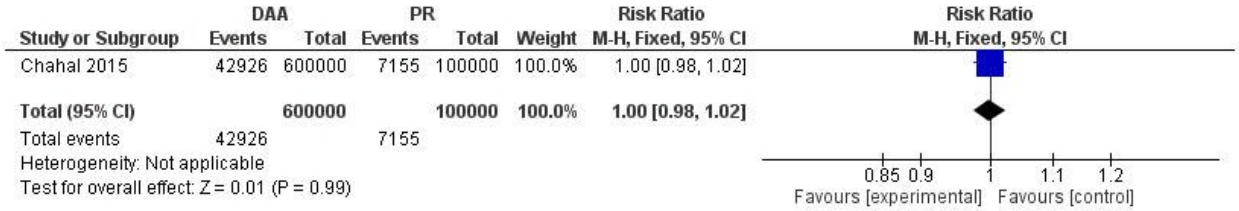
Hepatocellular Carcinoma – F2-F3

Study or Subgroup	DAA Events	DAA Total	PR Events	PR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chahal 2015	42575	1200000	10621	200000	100.0%	0.67 [0.65, 0.68]
Total (95% CI)		**1200000**		**200000**	**100.0%**	**0.67 [0.65, 0.68]**
Total events	42575		10621			

Heterogeneity: Not applicable
Test for overall effect: Z = 38.14 (P < 0.00001)

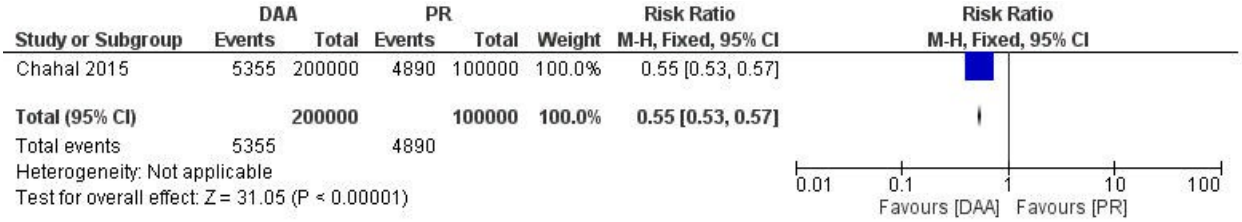


Hepatocellular Carcinoma – F4

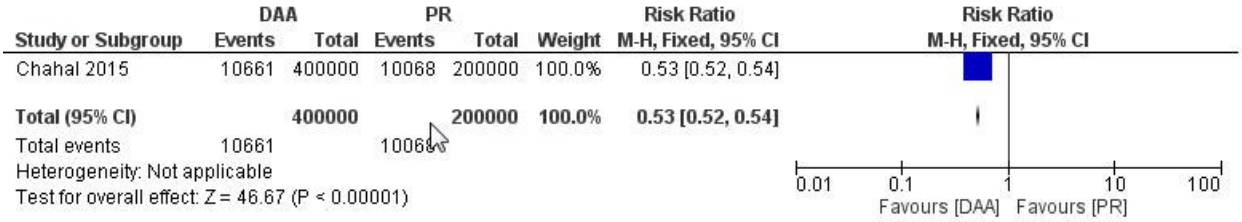


Q1.4a Sofosbuvir+Ledipasvir versus PR

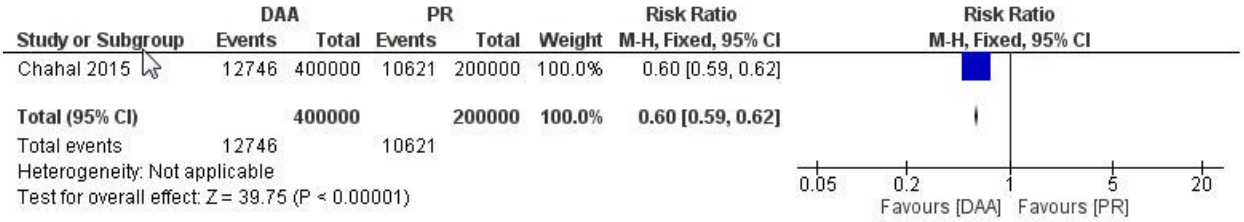
Hepatocellular Carcinoma



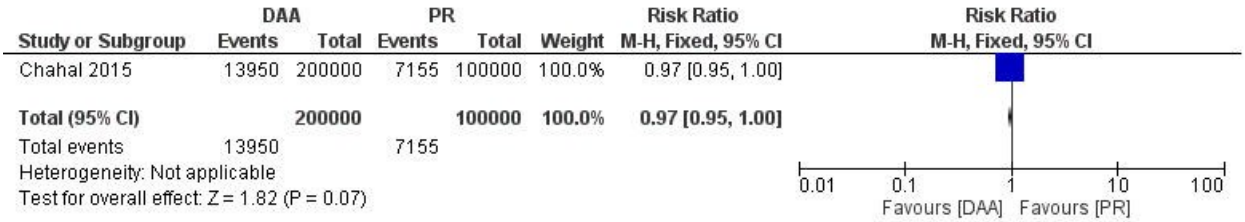
Hepatocellular Carcinoma – F0-F1



Hepatocellular Carcinoma – F2-F3

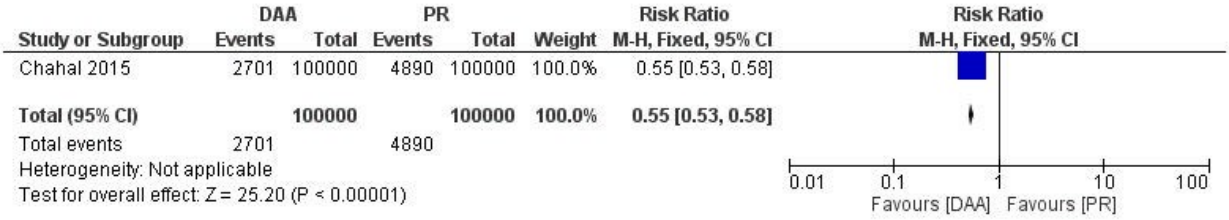


Hepatocellular Carcinoma – F4

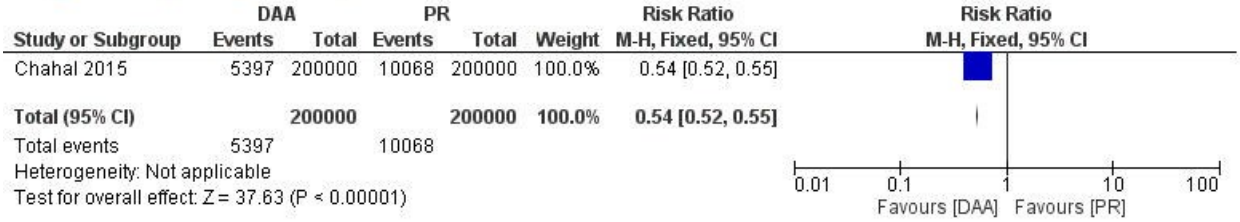


Q1.4b Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir ± Ribavirin (3D±Ribavirin) versus PR

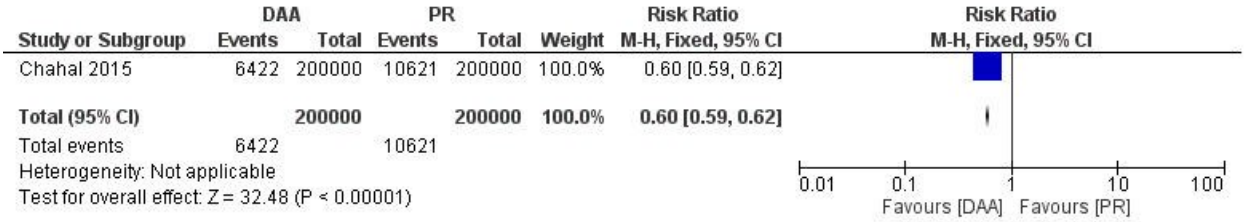
Hepatocellular Carcinoma



Hepatocellular Carcinoma – F0-F1



Hepatocellular Carcinoma – F2-F3

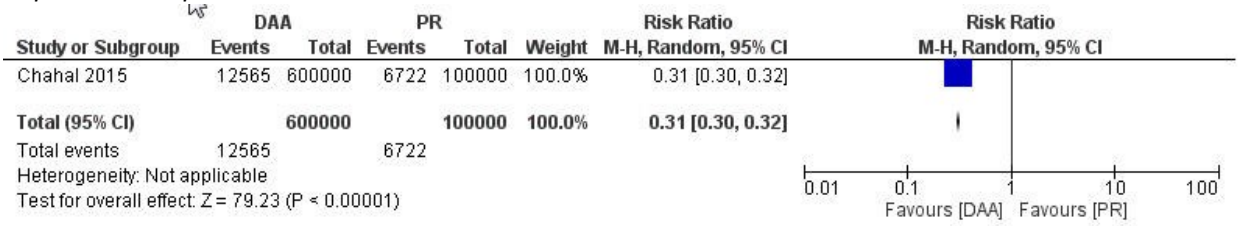


Hepatocellular Carcinoma – F4

Q1.5 Hepatic Decompensation

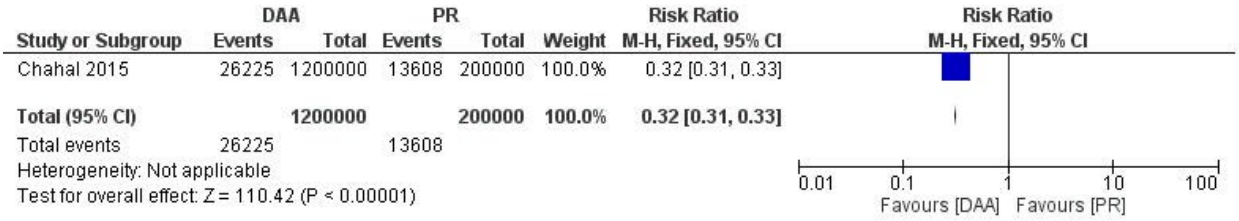
Q1.5 DAA versus PR

Hepatic Decompensation

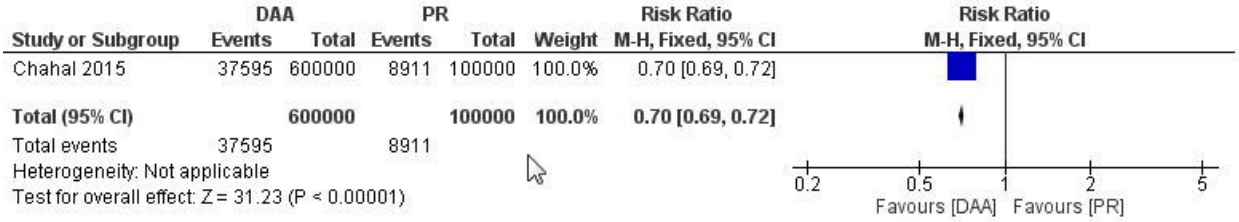


Hepatic Decompensation – F0-F1

Hepatic Decompensation – F2-F3

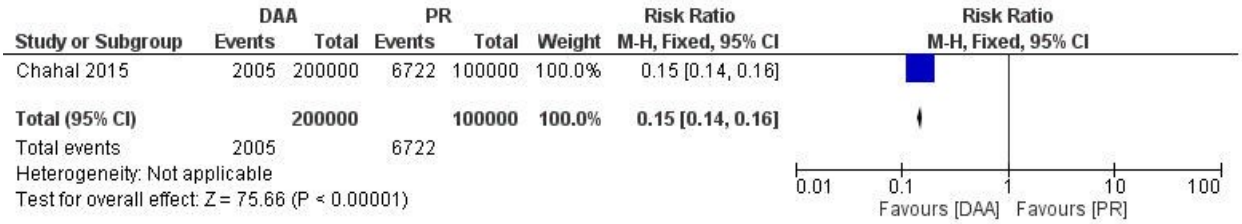


Hepatic Decompensation – F4

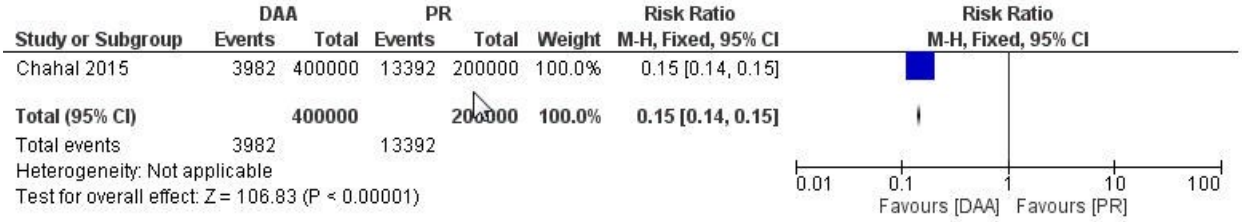


<u>Q1.5a Sofosbuvir+Ledipasvir versus PR</u>

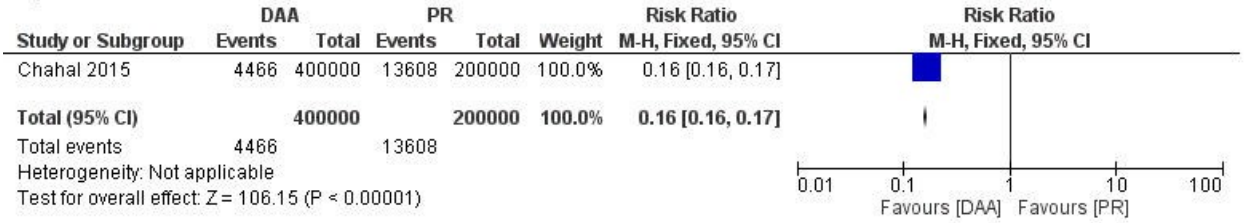
Hepatic Decompensation



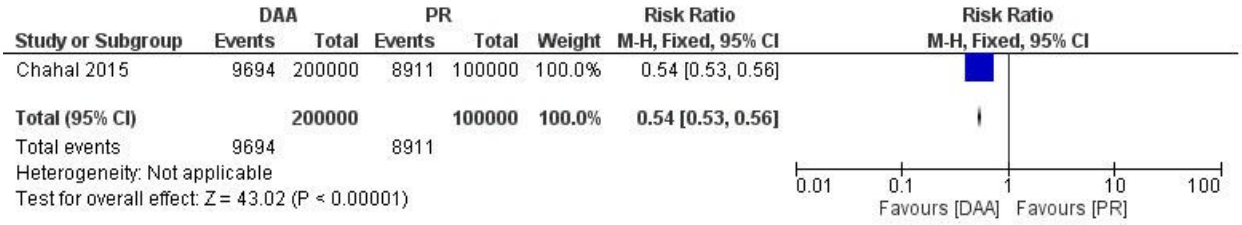
Hepatic Decompensation – F0-F1



Hepatic Decompensation – F2-F3

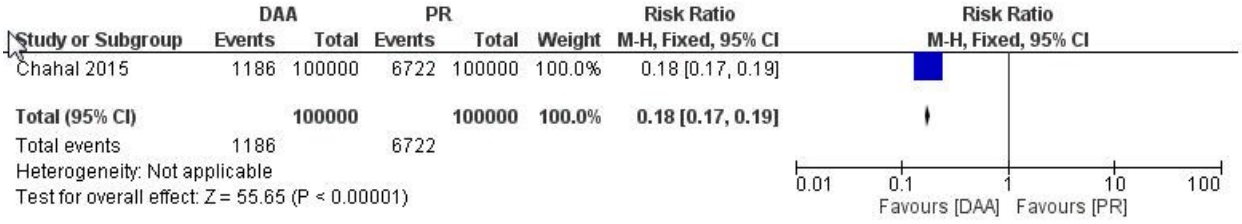


Hepatic Decompensation – F4

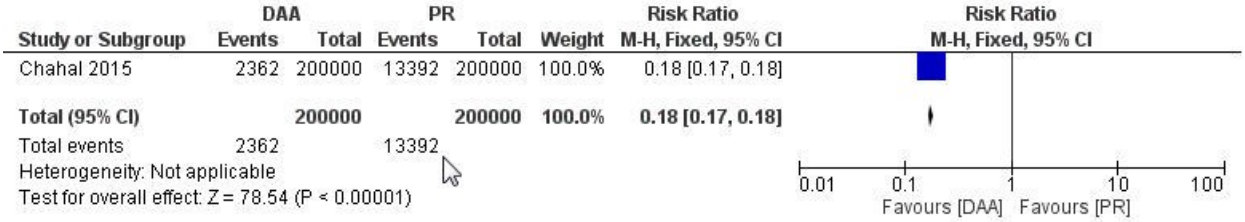


<u>Q1.5b Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir ± Ribavirin (3D±Ribavirin) versus PR</u>

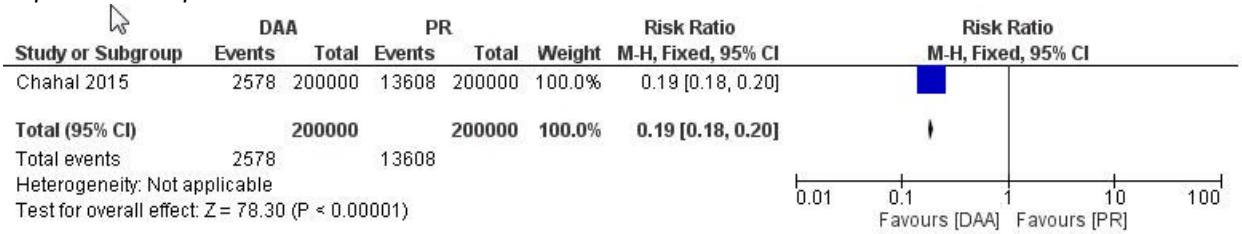
Hepatic Decompensation



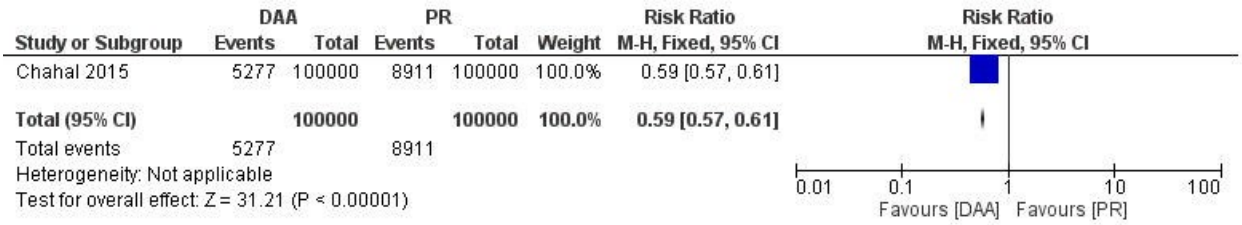
Hepatic Decompensation – F0-F1



Hepatic Decompensation – F2-F3



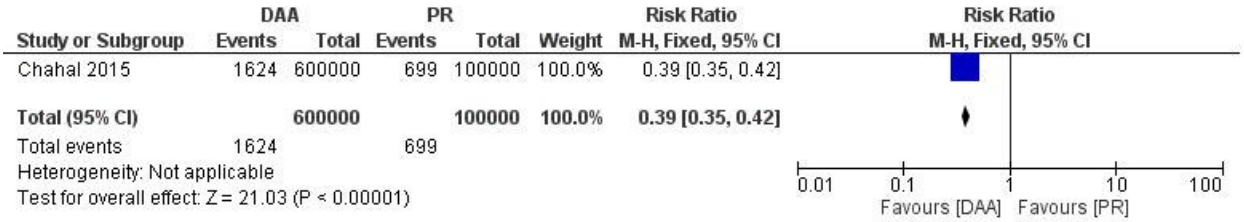
Hepatic Decompensation – F4



Q1.6 Need for Liver Transplantation

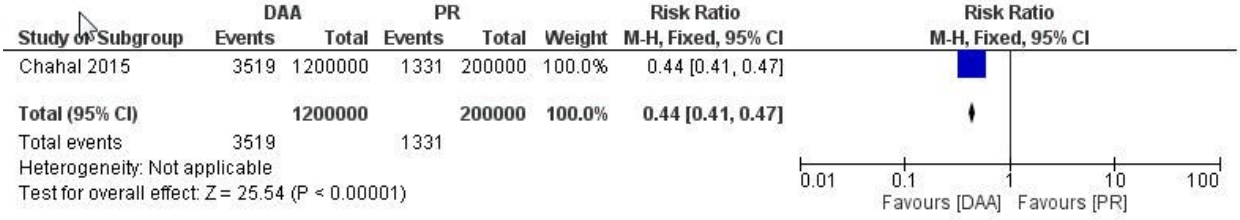
Q1.6 DAA versus PR

Need for Liver Transplantation

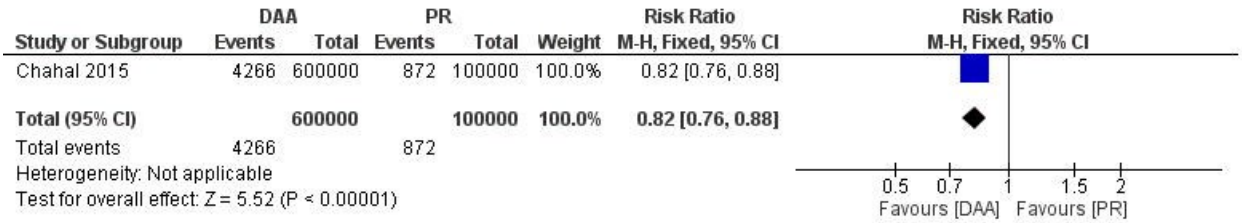


Need for Liver Transplantation – F0-F1

Need for Liver Transplantation – F2-F3

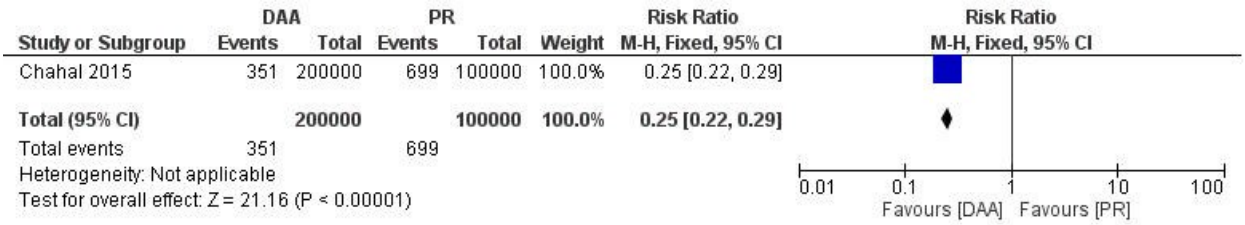


Need for Liver Transplantation – F4

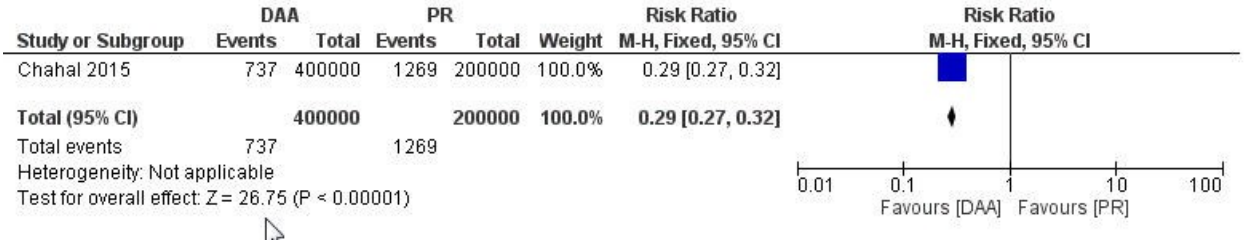


Q1.6a Sofosbuvir+Ledipasvir versus PR

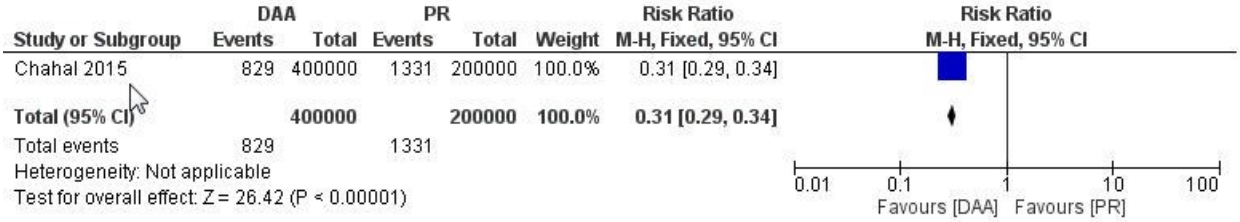
Need for Liver Transplantation



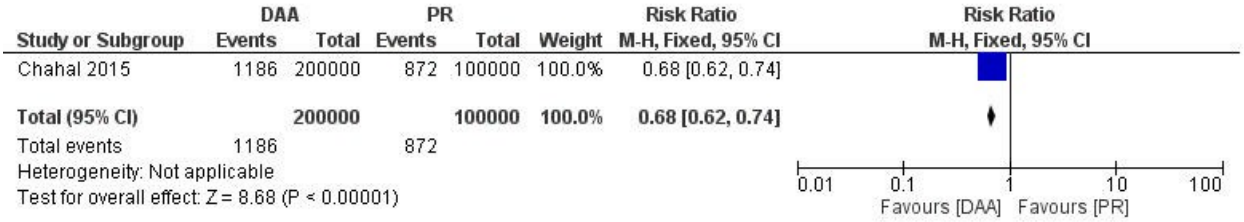
Need for Liver Transplantation – F0-F1



Need for Liver Transplantation – F2-F3

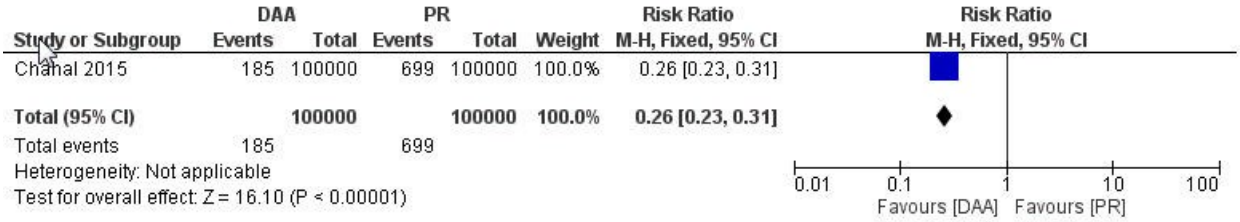


Need for Liver Transplantation – F4



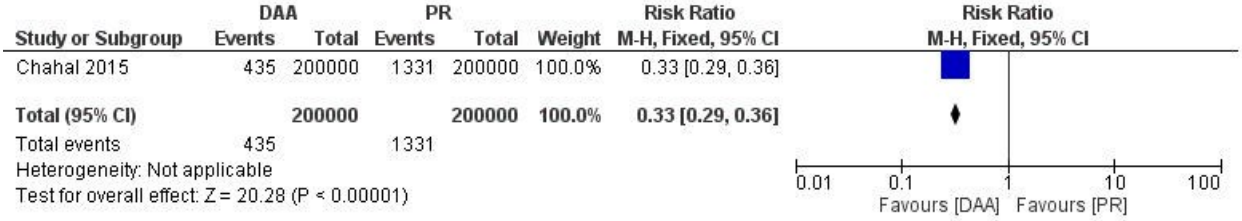
<u>Q1.6b Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir ± Ribavirin (3D±Ribavirin) versus PR</u>

Need for Liver Transplantation

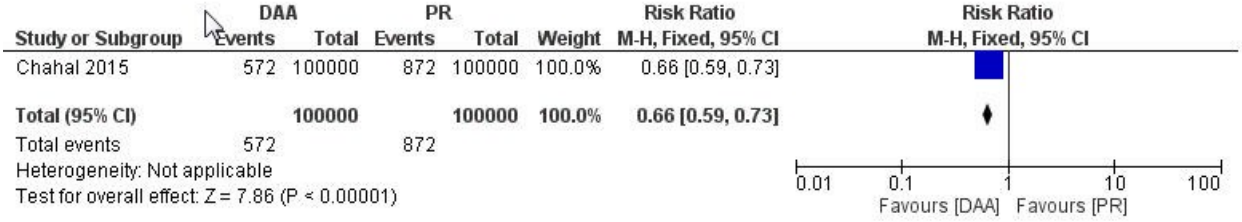


Need for Liver Transplantation – F0-F1

Need for Liver Transplantation – F2-F3

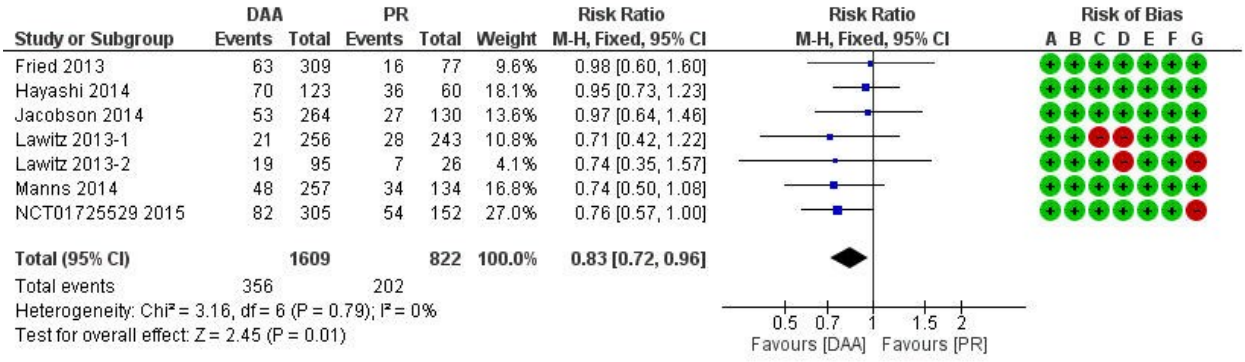


Need for Liver Transplantation – F4

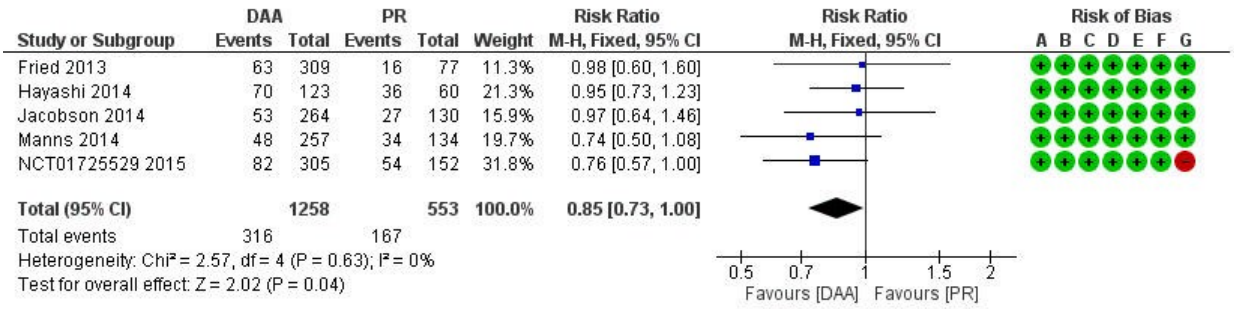


Q2.1 Anemia

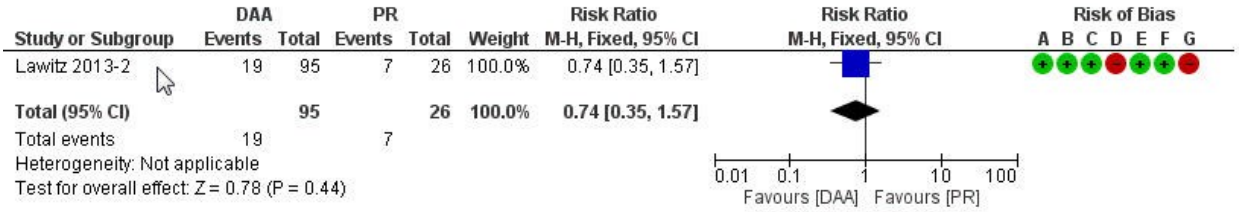
<u>Q2.1a DAA versus PR</u>



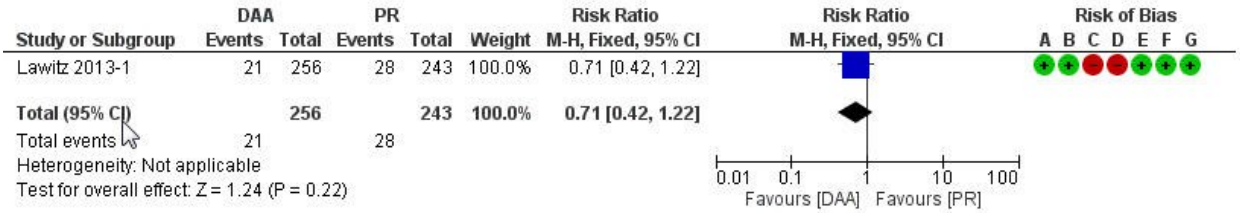
Q2.1b Simeprevir+PR versus PR



Q2.1c Sofosbuvir+PR versus PR

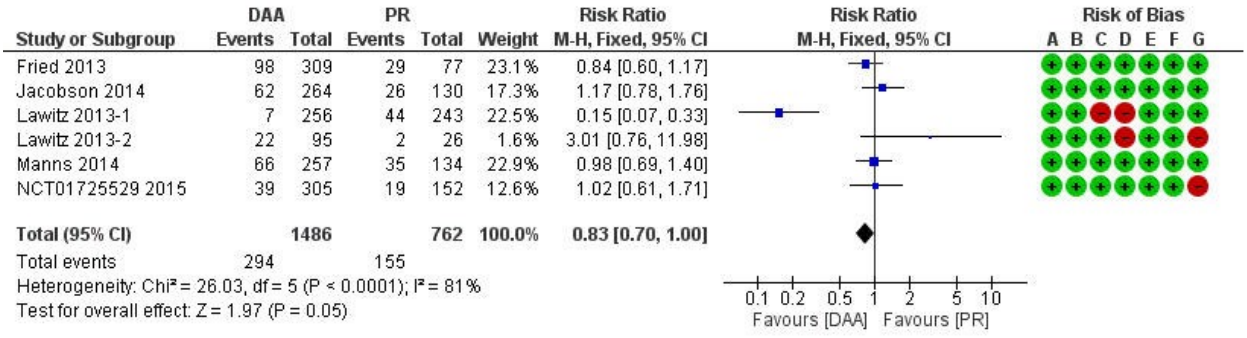


Q2.1d Sofosbuvir+Ribavirin versus PR

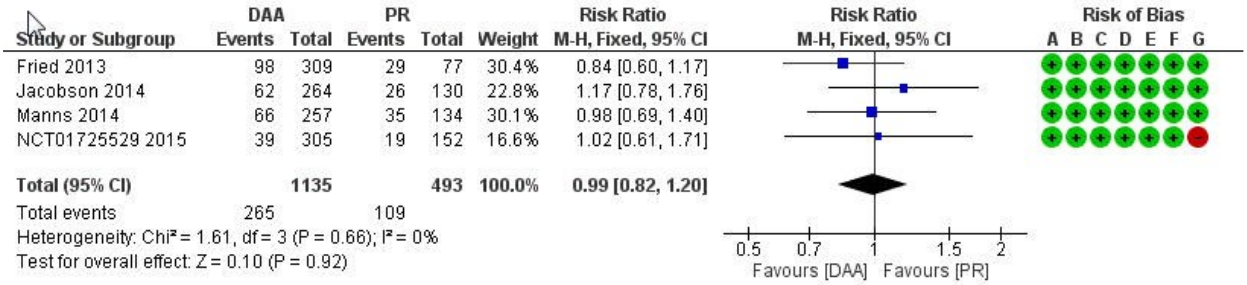


Q2.2 Flu-like Symptoms

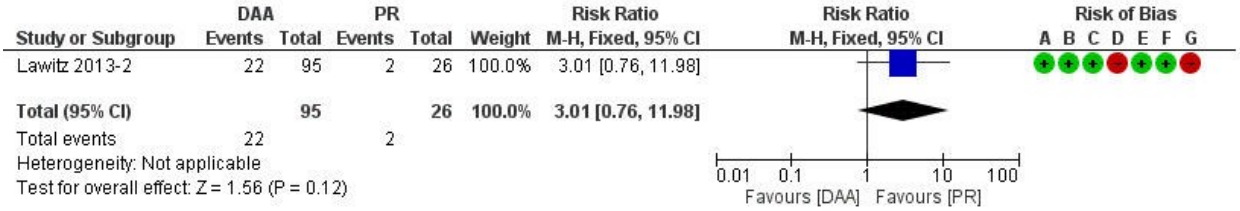
Q2.2a DAA versus PR



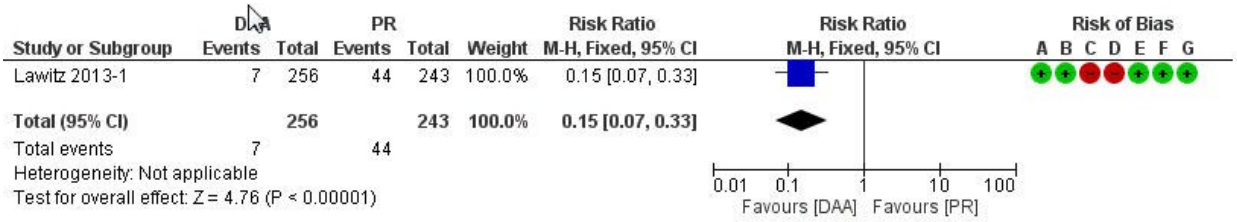
Q2.2b Simeprevir+PR versus PR



Q2.2c Sofosbuvir+PR versus PR

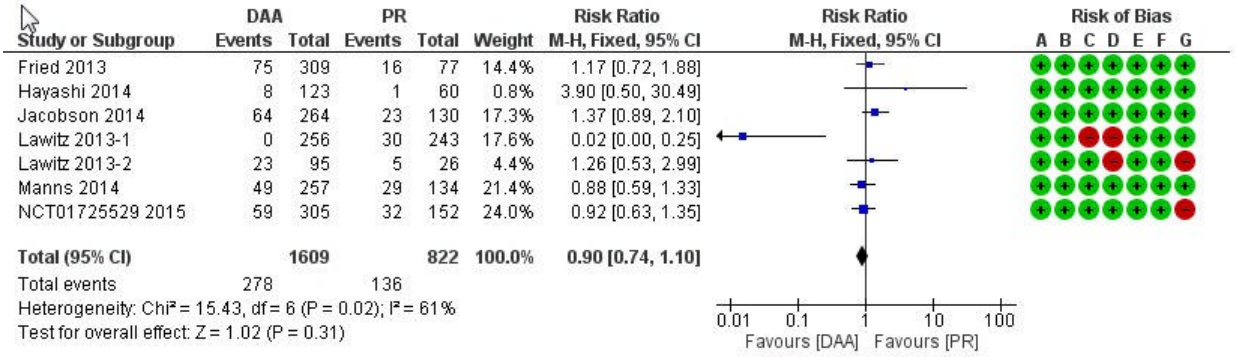


Q2.2d Sofosbuvir+Ribavirin versus PR

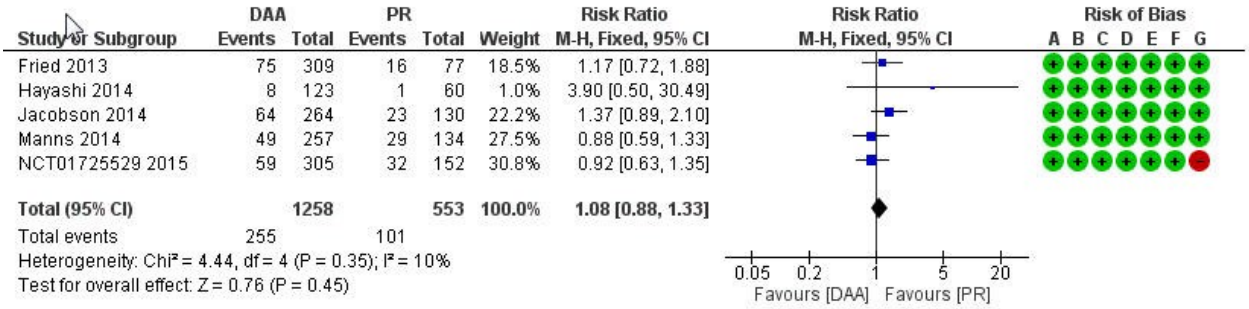


Q2.3 Neutropenia

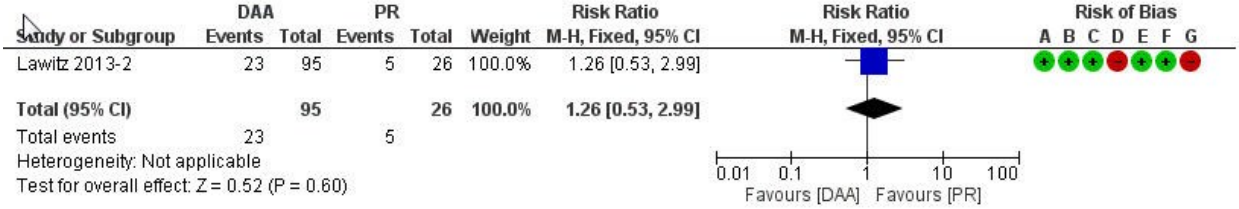
Q2.3a DAA versus PR



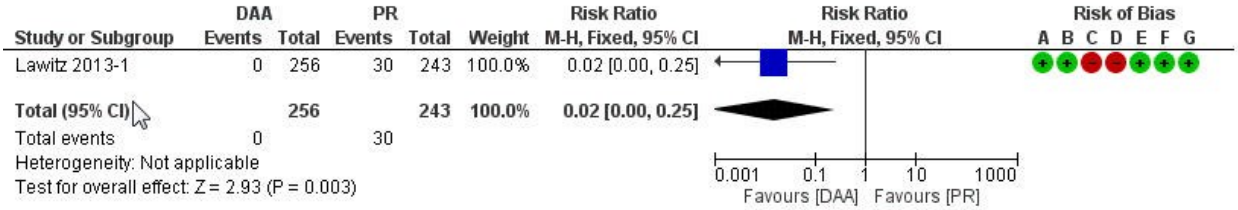
Q2.3b Simeprevir+PR versus PR



Q2.3c Sofosbuvir+PR versus PR

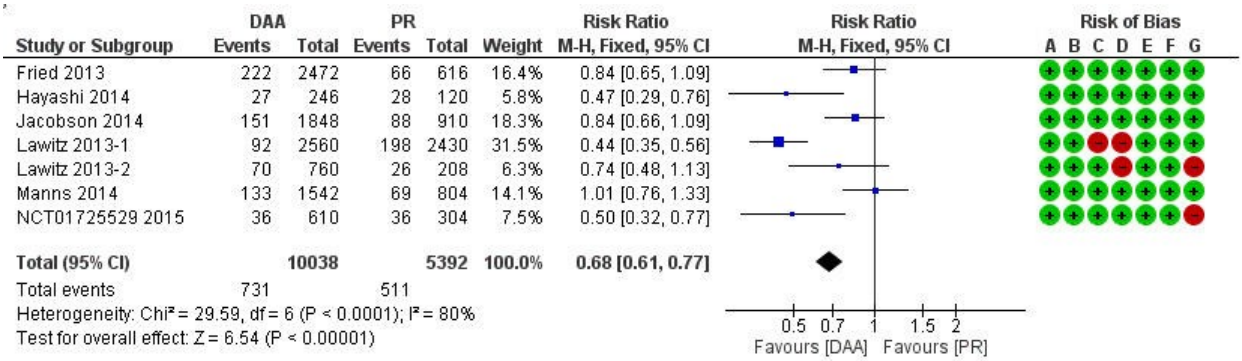


Q2.3d Sofosbuvir+Ribavirin versus PR

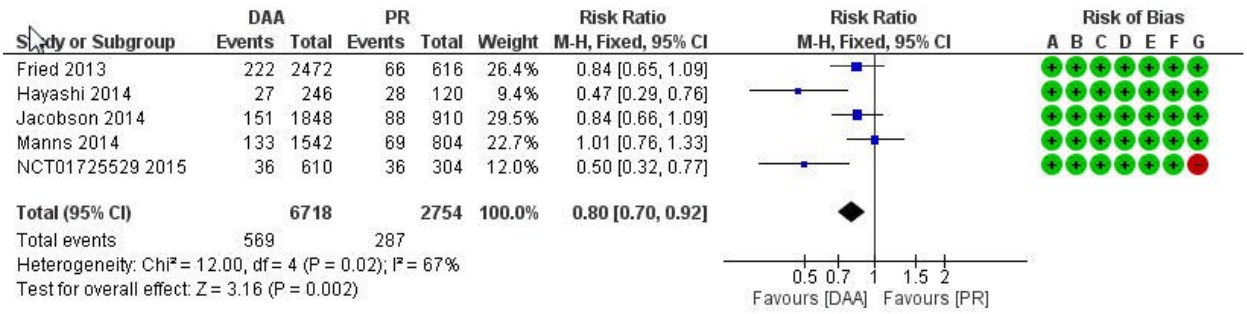


Q2.4 Psychological Adverse Events

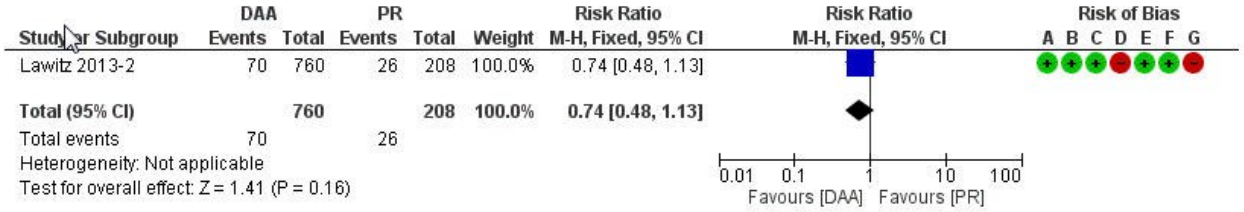
Q2.4a DAA versus PR



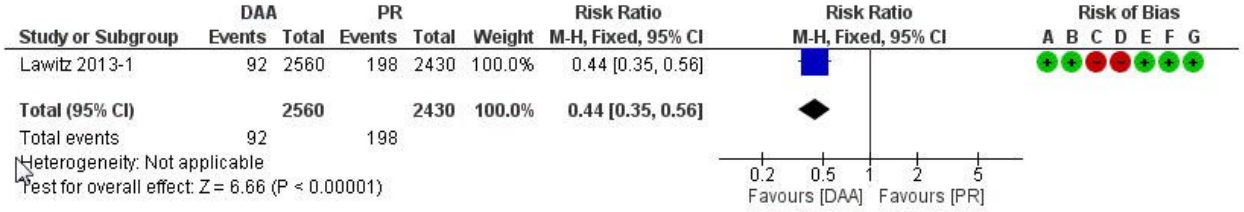
Q2.4b Simeprevir+PR versus PR



Q2.4c Sofosbuvir+PR versus PR

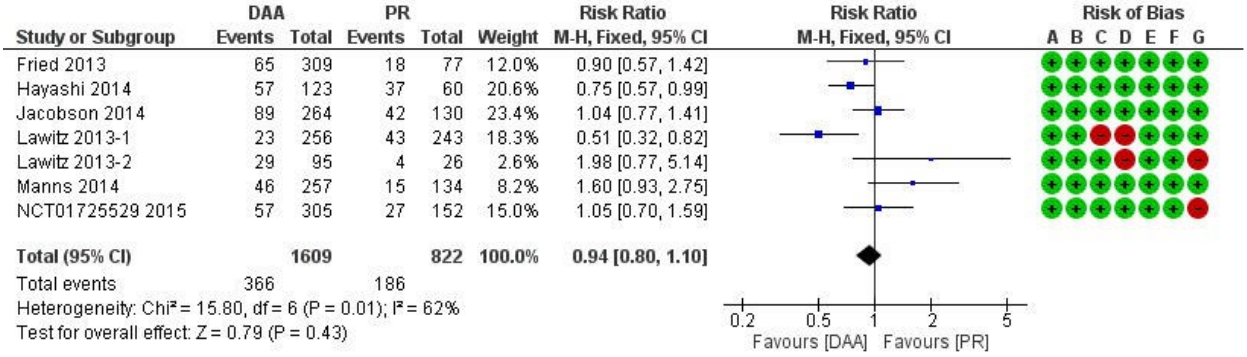


Q2.4d Sofosbuvir+Ribavirin versus PR

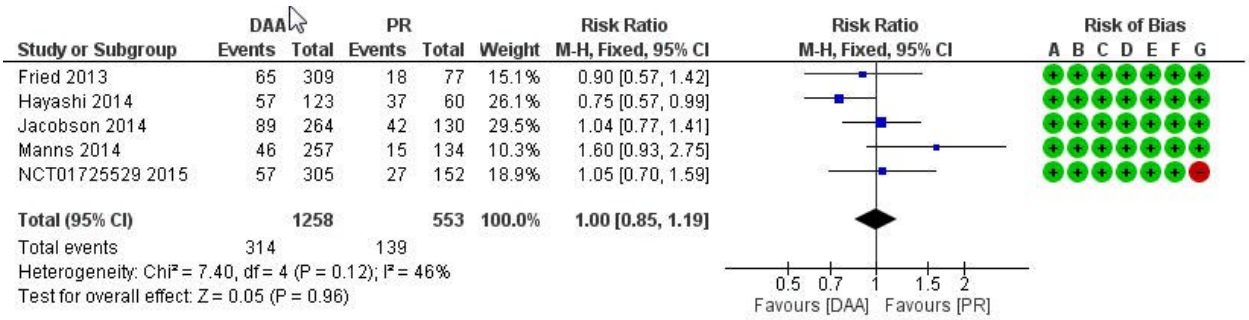


Q2.5 Rash

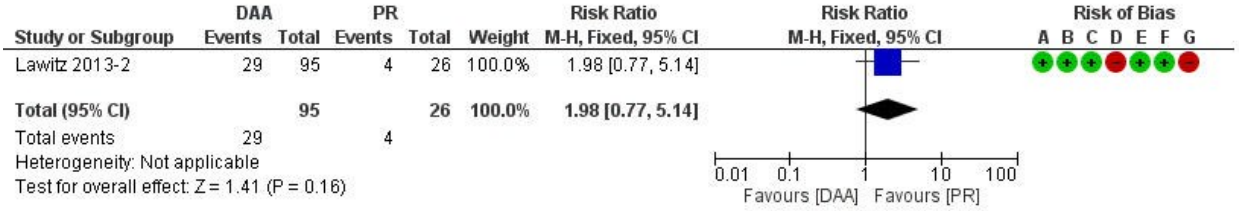
Q2.5a DAA versus PR



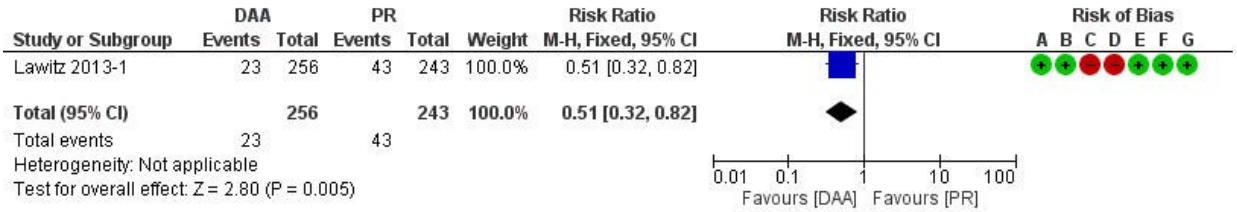
Q2.5b Simeprevir+PR versus PR



Q2.5c Sofosbuvir+PR versus PR

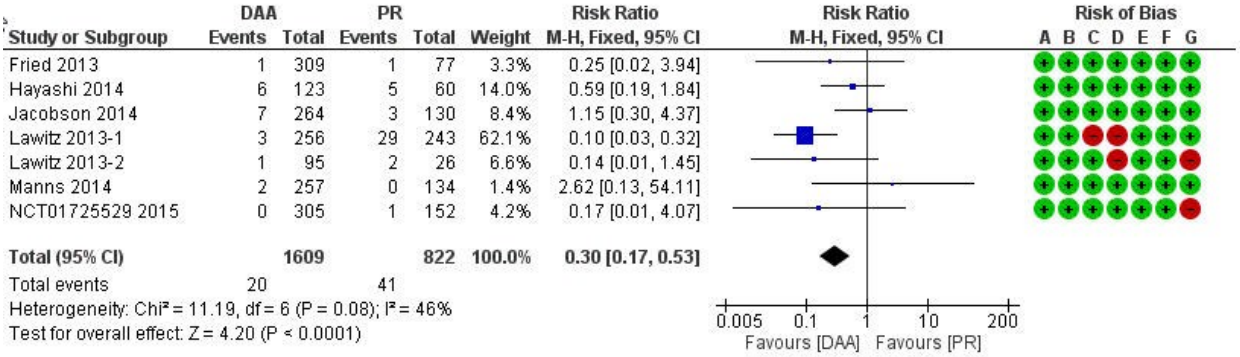


Q2.5d Sofosbuvir+Ribavirin versus PR

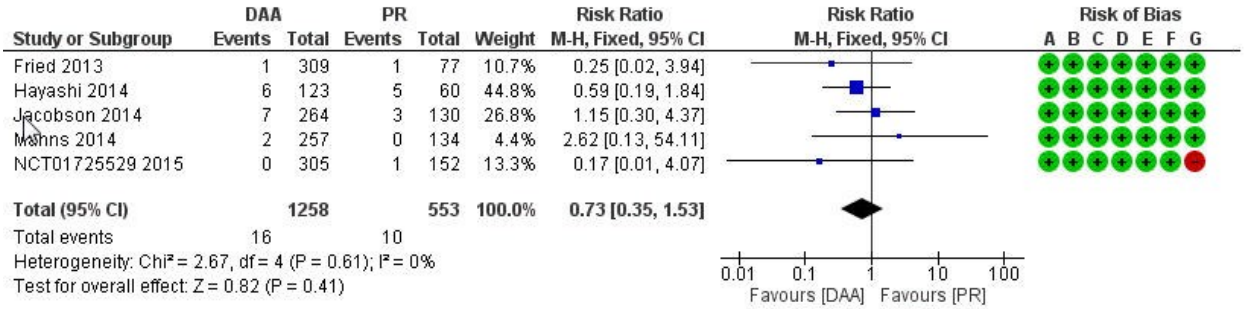


Q2.6 Withdrawals due to Adverse Events

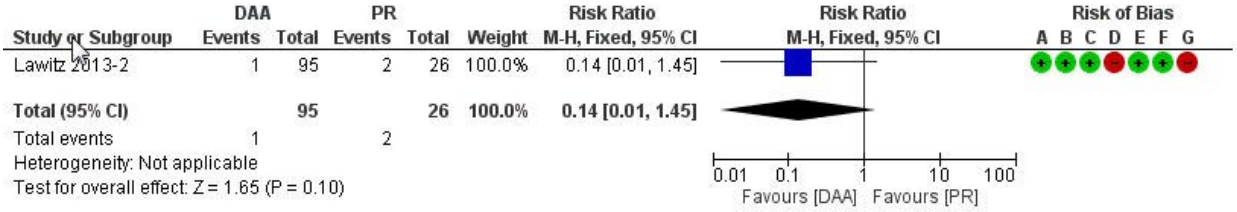
Q2.6a DAA versus PR



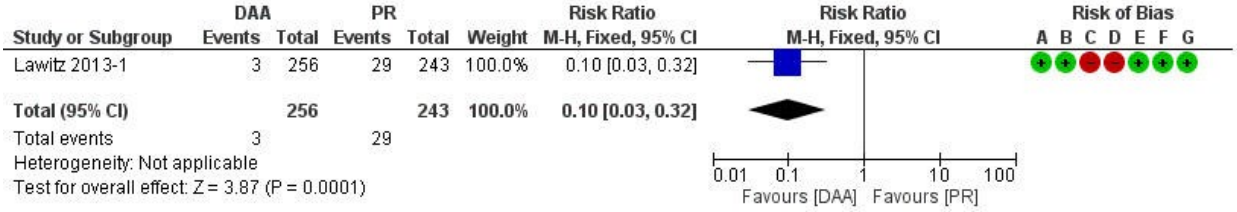
Q2.6b Simeprevir+PR versus PR



Q2.6c Sofosbuvir+PR versus PR



Q2.6d Sofosbuvir+Ribavirin versus PR



Appendix M

Comparing Long Term Outcomes by no Treatment and Treatment with Pegylated Interferon plus Ribavirin (PR) in Chahal 2016[38] Model based on treating 100,000 individuals

Treatment regimen	Decompensated cirrhosis	Hepatocellular carcinoma	Need for liver transplant	Hepatic mortality	Total
No treatment	14,091	8,337	1,347	21,111	44,886
PR	6,722	4,890	699	10,990	23,301
Sofosbuvir+PR	2,345	3,208	296	5,318	11,167
Sofosbuvir+ribavirin	5,708	4,551	615	9,722	20,596
Simeprevir+sofosbuvir	1,321	2,641	177	3,823	7,962
Sofosbuvir ledipasvir (8/12 weeks)*	1,119	2,698	184	3,700	7,701
Sofosbuvir ledipasvir (12 weeks only)	886	2,657	167	3,442	7,152
Ombitasvir/paritaprevir/ritonavir+dasabuvir	1,186	2,701	185	3,751	7,823

*For modelled individuals with F0-F3, 67% were treated for 8 weeks and 33% were treated for 12 weeks. For modelled individuals with F4, all were treated for 12 weeks

Treatment Durations by Treatment Regimens

Treatment Regimen	**Treatment Duration**
PR	48 weeks
Sofosbuvir+PR	12 weeks
Sofosbuvir+ simeprevir (interferon-free)	F0-F3 –12 weeks, F4 –24 weeks
Sofosbuvir+ ledipasvir (interferon-free) -1*	F0-F3 –67% of patients 8 weeks, 33% 12 weeks; F4 12 weeks
Sofosbuvir+ ledipasvir (interferon-free) -2*	12 weeks
Sofosbuvir+ ribavirin (interferon-free)	24 weeks
Ombitasvir/paritaprevir/ritonavir+dasabuvir ± ribavirin (interferon-free)	Genotype 1a, F0-F3 –12 weeks and Genotype 1a, F4 -24 weeks – all with ribavirin. Genotype 1b, F0-F3 - 12 weeks, without ribavirin; Genotype 1b, F4 12 weeks, with ribavirin.

* The model included two scenarios for SOF+LDV. These results have been combined in this systematic review.

Appendix N

Number and percentage of individuals achieving SVR 12 by treatment regimen

SVR 12- Manns (2014)[31]		
METAVIR Score	PR	DAA
F0-F2	51/102 (51%)[2]	165/195 (85%)
F3-F4	15/32 (47%)	35/53 (66%)
SVR 12- Jacobson (2014) [30]		
METAVIR Score	PR	DAA
F0-F2	54/90 (60%)	152/183 (83%)
F3-F4	11/40 (28%)	54/77 (70%)

[2] Represents number of people achieving SVR/number of people with pertinent fibrosis score and percentage who have achieved SVR in brackets

Appendix O

Achievement of SVR 24 by Treatment Regimen

Study	PR	DAA
Fried 2013[28] The Randomized PILLAR Study	64.9%	Simeprevir 75 mg - 74.7% Simeprevir 150 mg - 86.1%
Hayashi 2014[29], CONCERTO-1 trial	56.7%	Simeprevir 100 mg - 88.6%
Jacobson 2014[30], QUEST-1	49.2%	Simeprevir 150 mg - 79.5%
Lawitz 2013-1[36], FISSION trial	65.4%	Sofosbuvir 400 mg - 66.8%
Lawitz 2013-2[37], NCT01188772 trial	(Genotype 1) - 57.7	Sofosbuvir 200 mg (Genotype 1) - 89.6% Sofosbuvir 400 mg (Genotype 1) - 91.5% Sofosbuvir 400 mg (Genotype 2/3 - 92.0%
Manns 2014[31], QUEST-2 trial	50%	Simeprevir 150 mg - 80.5%
NCT01725529 2015[32], TIGER Trial	74%	Simeprevir 100 mg - 88.9% Simeprevir 150 mg - 90.8%