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Sofosbuvir for treating chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

V Copley (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; G Frampton (Senior Research Fellow) critically appraised the clinical effectiveness review, drafted the report and project managed the review; K Pickett (Research Fellow) critically appraised the clinical effectiveness review and drafted the report; E Loveman (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation, drafted the report, and is the project guarantor; K Cooper (Senior Research Fellow) critically appraised the mixed treatment comparison and the economic evaluation and drafted the report.

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[redacted].

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LIST OF ABBREVIATIONS

AE	Adverse event(s)
CC	Compensated cirrhosis
CEA	Cost effectiveness analysis
CLDQ-HCV	Chronic Liver Disease Questionnaire – Hepatitis C
CRD	Centre for Reviews and Dissemination
DC	Decompensated cirrhosis
DSA	Deterministic sensitivity analysis
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
ERG	Evidence review group
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
GT	Genotype
IFN	Interferon
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
MS	Manufacturer's submission
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PEG	Pegylated interferon alfa
PEG2a	Pegylated interferon alfa-2a (peginterferon alfa-2a)
PEG2b	Pegylated interferon alfa-2b (peginterferon alfa-2b)
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
pTVR	Post-transplant virologic response
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RBV	Ribavirin
RNA	Ribonucleic acid
SF-36	Short form 36
SOF	Sofosbuvir
TE	Treatment experienced
TN	Treatment naive
SmPC	Summary of product characteristics
SVR	Sustained virologic response
WPAI	Work Productivity and Activity Impairment

SUMMARY

Scope of the manufacturer submission

The manufacturer's submission (MS) reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to consider sofosbuvir in combination with ribavirin with or without peginterferon alfa for the treatment of chronic hepatitis C.

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from:

- Eight RCTs (four phase 3, four phase 2)
- Five non-randomised studies (two phase 3, three phase 2)

These studies report evidence for the following combinations of patients' hepatitis C virus (HCV) genotype and treatment history:

- HCV genotype 1, treatment naive (three phase 2 RCTs, one phase 3 non-randomised trial);
- HCV genotype 2/3, treatment naive (one phase 3 RCT, one phase 2 RCT and one phase 2 non-randomised trial) – the phase 3 RCT is a head-to-head trial of sofosbuvir against standard of care (ribavirin plus peginterferon alfa)
- HCV genotype 2/3, treatment experienced (one phase 3 RCT, one phase 2 non-randomised trial);
- HCV genotype 2/3, treatment naive and experienced (two phase 3 RCTs of which one was converted to a non-randomised multi-cohort trial);
- HCV genotypes 1/2/3, treatment naive and experienced, with HCV and HIV co-infection (one phase 3 non-randomised trial);
- Patients with any HCV genotype, awaiting a liver transplant (one phase 2 non-randomised trial) – this trial was not used to inform the economic analysis.

Sofosbuvir is licensed for use in combination with ribavirin with or without peginterferon alfa-2a or peginterferon alfa-2b, for either 12 or 24 weeks of therapy depending upon the patient's HCV genotype and treatment history. Due to the licensed indications for sofosbuvir being HCV-genotype-specific, some of the patient groups listed above have more than one licensed sofosbuvir regimen.

The primary outcome is sustained virologic response, expressed as the proportion of patients (%) who achieved an undetectable level of HCV RNA 12 weeks after the end of treatment (SVR12). SVR12 is reported for each of the patient groups listed above and in some cases also for subgroups of patients within these.

SVR12 rates in sofosbuvir regimens of the included studies ranged from [redacted] to 100%, depending upon the regimen, duration of therapy, and treatment history of the patients:

- HCV genotype 1, treatment naïve: SVR12 ranged from 52% to 93%.
- HCV genotype 2/3 combined: SVR12 ranged from 50% to 100% (in studies on mixed treatment naive and experienced, and treatment naive patients respectively).
- HCV genotype 2 subgroup: SVR12 ranged from 86% to 100% (in studies on treatment experienced and treatment naive patients respectively).
- HCV genotype 3 subgroup: SVR12 ranged from [redacted] to 100% (in studies on treatment experienced and treatment naive patients respectively).
- HCV genotypes 1/2/3, treatment naive and experienced, with HCV and HIV co-infection (a subgroup specified in the NICE scope): SVR ranged from 67% to 93%.

Only one RCT provided a direct head-to-head comparison of sofosbuvir against standard of care (peginterferon alfa + ribavirin) as specified in the NICE scope, for HCV genotype 2/3 treatment naive patients; SVR12 was found to be 67% following sofosbuvir + ribavirin for 12 weeks and also 67% following peginterferon alfa-2a + ribavirin for 24 weeks.

The NICE scope specifies that subgroup analysis of SVR12 rates according to patients' response to prior therapy should be considered. Three studies provided relevant subgroup analyses:

- interferon non-responders versus those with relapse or virologic breakthrough (one trial – found no differences in SVR12 between the subgroups);
- interferon-ineligible patients versus those classified as interferon-intolerant or interferon-unwilling (one trial - found no differences in SVR12 between the subgroups);
- interferon-intolerant patients versus interferon-non-responders and those with relapse or virologic breakthrough
  ([redacted])

Subgroup analysis of SVR12 according to the presence or absence of cirrhosis is not specified in the NICE scope but is considered by the ERG since the presence or absence of cirrhosis is included as a key variable in the manufacturer's economic analysis.

Other outcomes included health related quality of life (HRQoL) and adverse events.

HRQoL was assessed in five studies. Several domains of HRQoL were negatively affected by sofosbuvir-based therapy but HRQoL scores generally returned to pre-treatment levels after therapy ended. The decrement in HRQoL during sofosbuvir-based therapy was smaller than during peginterferon alfa + ribavirin therapy (assessed in one trial only), and compared against an inactive placebo sofosbuvir + ribavirin did not result in worse HRQoL during therapy (assessed in one trial only).

Adverse events are reported in the MS from five of the phase 3 studies but not any phase 2 studies. The ERG checked that adverse events reported in phase 2 studies were in agreement with those in the phase 3 studies. Overall, sofosbuvir-based regimens were generally well tolerated and resulted in fewer adverse events than were seen with peginterferon alfa + ribavirin.

Summary of submitted cost effectiveness evidence

The manufacturer's submission to NICE includes:

- A systematic review of published economic evaluations of treatments for HCV.
- A report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of sofosbuvir and ribavirin with or without peginteferon alfa is reported in different HCV genotype subgroups compared to: peginterferon alfa + ribavirin; telaprevir + peginteferon alfa + ribavirin; and boceprevir + peginterferon alfa + ribavirin, as appropriate to their respective licensed indications.

No relevant economic evaluations of sofosbuvir were identified in the systematic review. 112 studies of other treatments were included; however, there is limited discussion in the MS about the included studies overall, and no general conclusions about the findings of the systematic review are provided.

The economic evaluation uses a Markov model to estimate the cost-effectiveness of sofosbuvir for a number of different patient groups. The model adopted a lifetime horizon (until patients reach 100 years), with an annual cycle length (except in the first two years where a 3 month cycle was used). Patients enter the model from either a non-cirrhotic health state or a compensated cirrhosis (CC) health state. There are four other liver related health states (decompensated cirrhosis [DC], liver transplant, post liver transplant and hepatocellular carcinoma [HCC]) and a health state for death. Treatment effect data were based on the SVR12 rates taken from the sofosbuvir clinical trials and where data for SVRs of comparators were not available in the sofosbuvir trials these were taken from other studies identified by the manufacturer. The main determinants of quality of life in the model were taken from utilities from a UK mild chronic hepatitis C trial.

The MS presents base case results for HCV genotype subgroups, for treatment history (treatment naive or experienced) and eligibility for peginterferon-based treatment. In the NICE scope two subgroups were noted, co-infection with HIV and response to previous treatment (non-response, partial response, relapsed). Only the former subgroup was modelled. The MS reports that the model underwent internal and external validation.

Results of the manufacturer's model show that sofosbuvir is a cost-effective treatment option in the majority of subgroups presented. Base case ICERs were in most cases below £30,000 per QALY gained. The exceptions were HCV genotype 1 treatment naive patients who are unsuitable for peginterferon (ICER £49,249) and treatment naive patients with HCV genotype 2 (ICER £46,324). No analysis of HCV genotype 1 treatment experienced patients was undertaken in the original base case.

The MS undertook deterministic sensitivity analyses (DSA) on a range of variables and demonstrated that ICERS were most sensitive to the discount rates for costs and outcomes and the utility increment after achieving SVR. The MS DSA results show which genotype subgroups remain cost effective at a £20,000 per QALY gained for sofosbuvir against respective comparator treatments. The ERG generally agrees with the conclusions from the DSA.

The MS summarises the results of a probabilistic sensitivity analysis (PSA) stating that there is a range of probabilities of sofosbuvir being cost-effective at a threshold willingness to pay (WTP) threshold of £20,000 and £30,000 per QALY gained. The MS does not draw any general

conclusions from the results of the PSA. The ERG concludes that at a threshold of £20,000 per QALY sofosbuvir is not cost effective in six of the base case comparisons as it has a probability of cost-effectiveness of less than 50%. At a threshold of £30,000 per QALY sofosbuvir is not cost effective in four of the base case comparisons.

In general the ERG considers that the modelling approach adopted in the submission is reasonable and is consistent with the sources of evidence used in its development. One limitation is that a transition is not included from the SVR-Cirrhotic to the HCC health state.

The clinical effectiveness parameters used in the model are generally reasonable. It would have been preferable to use a weighted average of male and female all-cause mortality to better reflect the balance between the sexes seen in clinical practice. The MS does not justify its assertion that the SVRs seen in the key studies for mono-infected and HIV co-infected populations are similar.

Commentary on the robustness of submitted evidence

Strengths

- The MS contains systematic searches for the clinical and cost-effectiveness studies of sofosbuvir. It appears unlikely that these would have missed any studies that would have met the inclusion criteria.
- The systematic review meets most of the NICE recommended criteria for methodological quality.
- The economic model presented in the MS used an appropriate approach for the disease area.
- Apart from some specific differences (noted below), the economic model used a similar structure and parameter inputs to those used in previous economic models of chronic hepatitis C developed for NICE.

Weaknesses and Areas of uncertainty

- There is only one head-to-head trial comparing sofosbuvir-based therapy with a comparator as specified in the NICE scope (peginterferon alfa-2a + ribavirin); this is in HCV genotype 2/3 treatment naive patients.

- No clinical trial data are available for the efficacy of sofosbuvir in comparison to the protease inhibitors boceprevir and telaprevir in treating genotype 1 patients as specified in the NICE scope.
- No clinical trial data are available for treatment experienced patients with HCV genotype 1 infection; this is an unmet need group, without alternative non-interferon therapy options.
- Where SVR12 rates are available for specific genotypes (i.e. consistent with the licensed indications for sofosbuvir), these are mostly from subgroup analyses which in some cases have small sample sizes.
- Analyses of subgroups were not powered statistically to detect differences among subgroups.
- The economic model structure is modified from a structure used in previous HTAs for HCV and replaces 'mild', 'moderate', and 'severe' cirrhosis health states with 'non-cirrhotic' and 'cirrhotic'. As a consequence SVRs are required for each of these health states but there is a paucity of data in the literature to fulfil the requirements of the model. The clinical efficacy data may therefore not be robust.
- Direct evidence of sofosbuvir versus comparators is lacking and in most cases efficacy data come from single arms of a variety of RCTs (or non-RCTs).
- The ERG was unable to check all efficacy and transition probability data used in the MS and some calculations were not sufficiently well presented to allow replication.
- The model is not well validated against external data. This is particularly the case with the comparison with boceprevir+PEG2b+RBV where the MS model outcomes do not agree with previously presented results for this treatment.

Summary of additional work undertaken by the ERG

- Validation work was undertaken to compare the results of the sofosbuvir model to previous HTA models.
- PSA was re-run for all indications and comparators considered in the base case as the ERG found a slight error in the settings of the model slider control used to set the probability of cost-effectiveness at the £20,000 and £30,000 WTP thresholds.
- The model was re-run to examine variation to the final ICERs caused by using alternative estimates of SVR for PEG2a+RBV in the HCV genotype 1 treatment naive interferon eligible population.

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- The effect of using PEG2a cost data on the cost-effectiveness of boceprevir was examined
- The manufacturer's analysis including a transition from SVR-Cirrhotic to the HCC health state was examined and verified.
- The model was re-run with a discount rate of 1.5% for costs and outcomes.
- The effect of variation to all-cause mortality probabilities was assessed.
- The manufacturer's exploratory analysis in an HCV genotype1 treatment experienced population was verified.
- PEG2b and Rebetol costs were applied in selected indications, instead of PEG2a and Copegus costs.

The sofosbuvir model is broadly consistent with previous HTAs in terms of PEG+RBV total costs and QALYs, and with telaprevir total costs and QALYs. There is a relatively large discrepancy between models in boceprevir total costs. The base case results persist when the model is altered to include a transition from the SVR-Cirrhotic to the HCC state. The base case results are also generally robust to other changes except that: sofosbuvir becomes cost-effective at a WTP of £20,000 per QALY in four of the base case treatment comparisons when a discount rate of 1.5% is used (where it was not cost-effective in the base case); and sofosbuvir is no longer cost-effective compared to PEG2a+RBV in the GT1 treatment naïve interferon eligible indication at a WTP of £20,000 per QALY when alternative SVR estimates for PEG2a+RBV are used.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Gilead Sciences Inc. on the clinical effectiveness and cost effectiveness of sofosbuvir for chronic hepatitis C. It identifies the strengths and weaknesses of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 24 February 2014. A response from the manufacturer via NICE was received by the ERG on 18 March 2014 and this can be seen in the NICE Committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear and accurate overview of chronic hepatitis C.

2.2 Critique of manufacturer's overview of current service provision

The MS provides a clear and accurate overview of the current treatment options and clinical pathway for managing chronic hepatitis C in clinical practice, drawing on NICE clinical guidance (TA 253,[1] TA 252,[2] TA 200,[3] TA 106,[4] and TA 75[5]) and the European Association for the Study of the Liver (EASL) guidelines.[6] The MS also accurately details that a significant proportion of patients with chronic hepatitis C have unmet treatment needs, due to limitations of the current treatment options, and particularly highlights that there are currently no treatment options for patients who are unsuitable for interferon. The MS, however, does not describe all the patient groups where there are currently unmet needs. Clinical expert opinion to the ERG indicates that there is a need for more treatment options for treatment experienced genotype 1 patients and treatment experienced cirrhotic genotype 3 patients, but the unmet need for these groups are not mentioned in the overview of current service provision in the MS (although the high unmet treatment need for treatment experienced genotype 1 patients is mentioned later in the MS on p. 159).

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem – adults with chronic hepatitis C – is appropriate for the NHS and matches the broad chronic hepatitis C population described in final scope issued by NICE and the licensed indication for sofosbuvir, which is for use in adults only.[7]

Intervention

The intervention, sofosbuvir (SOF), is licensed for the treatment of chronic hepatitis C when administered together with ribavirin (RBV) (dual therapy) or when administered together with RBV and peginterferon-alfa (triple therapy). Sofosbuvir is not licensed as a monotherapy for chronic hepatitis C.[7] Sofosbuvir triple therapy is permitted with either peginterferon alfa-2a (PEG2a) or peginterferon alfa-2b (PEG2b) (which are considered equally efficacious[8;9]). However, in clinical studies, sofosbuvir triple therapy has so far only been combined with PEG2a. In this report, unless stated otherwise, the abbreviations SOF, PEG2a and RBV refer to the following standard dosing regimens of these therapies as specified in the summary of product characteristics (SmPC) for sofosbuvir[7] and peginterferon alfa-2a:[10]

- SOF: oral tablet, 400 mg once daily with food.
- RBV (Copegus®): oral tablet, twice daily to give a total weight-based dose per day of 1000 mg (if < 75 kg) or 1200 mg (if ≥ 75 kg) (note that Rebetol® is used specifically with PEG2b and as such is only referred to in this report where regimens containing PEG2b are being discussed).
- PEG2a, subcutaneous injection, 180µg once per week.

Sofosbuvir, a first-in-class uridine nucleotide, was granted its marketing authorisation in January 2014. In line with the final scope and licensed indication,[7] the intervention described in the decision problem is sofosbuvir either as a dual therapy (SOF+RBV) or triple therapy (SOF+PEG+RBV). The MS accurately details in Table 6 (MS p. 36) that treatment length and the choice of combination therapy depends on a patient's HCV genotype and whether or not a patient is suitable for interferon treatment. For patients with HCV genotypes 1 and 3 to 6, the licensed indication is sofosbuvir triple therapy for 12 weeks. When sofosbuvir is used in triple therapy, the SmPC[7] states that the treatment duration can be extended beyond 12 weeks and up to 24 weeks, if a patient has a risk factor associated with a poorer response to interferon-based therapies, such as cirrhosis. For genotype 3, sofosbuvir dual therapy can also be used, for a treatment period 24 weeks. For genotype 2, the only licensed sofosbuvir treatment is

sofosbuvir dual therapy for a treatment period of 12 weeks (and can be extended up to 24 weeks for the same reasons as above). Sofosbuvir dual therapy, administered over 24 weeks, is only recommended for genotype 1, 4, 5 and 6 patients who are ineligible or intolerant to interferon-based therapy. The MS states that Sofosbuvir can also be used in patients with chronic hepatitis C awaiting liver transplantation and the duration of therapy is guided by the risks and benefits to individual patients – this matches the licensed indication, and the ERG notes that the SmPC states that sofosbuvir can only be used as dual therapy in this group.

The description of the intervention in the MS is appropriate for the NHS and, as set out in the MS, sofosbuvir potentially offers a therapy option for some patients with chronic hepatitis C who currently have unmet treatment needs, particularly for those who are not suitable for interferon treatment. However, the MS does not refer to the potential issue of deciding which patients would be interferon 'ineligible' (clinical experts suggested that patients do not like interferon-based therapies and, given a choice, may decline interferon-based therapy).

Comparators

The manufacturer has included the following comparators in their decision problem (MS p. 51):

- Peginterferon alfa with ribavirin
- Telaprevir in combination with peginterferon alfa (for HCV genotype 1 only)
- Boceprevir in combination with peginterferon alfa and ribavirin (for HCV genotype 1 only)
- Best supportive care

The comparators described in the manufacturer's decision problem match those specified in NICE's final scope and reflect current clinical practice and the treatment options for chronic hepatitis C recommended for use in the NHS in TA 253,[1] TA 252,[2] TA 200,[3] TA 106[4] and TA 75.[5]

Outcomes

In line with NICE's final scope, the manufacturer has specified the following outcomes in their decision problem:

- Sustained virological response (SVR)
- Mortality

- Adverse effects of treatment
- Health-related quality of life

These outcomes are appropriate and clinically meaningful. The MS states successful treatment is indicated by an SVR defined as an "undetectable serum HVC RNA at 12 weeks after treatment has been stopped" (MS p. 15). The ERG notes that the 4 phase 3 RCTs included in the MS report measured SVR at 12 weeks post-treatment (SVR12) as the primary outcome and at 24 weeks post-treatment (SVR24) as a secondary outcome. The ERG considers SVR12 to be an appropriate endpoint. Historically, SVR24 has been used to measure patient response to therapy,[3] but recent research shows that SVR12 is highly predictive of SVR24[11;12] and SVR12 is now considered an appropriate endpoint for regulatory approval.[12] Clinical expert advice to the ERG suggests that relapse after successful treatment with sofosbuvir would be very unlikely to occur more than 8 weeks post treatment and, in clinical practice, monitoring of patient response would usually occur at 12 weeks after the end of treatment for both sofosbuvir and PEG2a in combination with RBV (the ERG notes, however, that a small proportion of patients may relapse after this time).

Economic analysis

The economic analysis proposed in the decision problem matches the final scope and is appropriate for the NHS. The manufacturer has used a lifetime horizon, which is appropriate for capturing differences in costs and outcomes for intervention in chronic hepatitis C.

Other relevant factors

The final scope specified that, if evidence allowed, the submission should consider subgroups of patients co-infected with HIV and subgroups according to patients' previous response to treatment (non-response, partial response, relapsed). The manufacturer has included these subgroups in their decision problem. The MS includes one trial on HIV co-infected patients, and information on SVR12 in previous response subgroups is available in 2 studies (of which one is mentioned in the MS) (see section 3.3.1 below). However, the subgroups on previous response to treatment are not used to inform the economic model.

The MS states that there are no known equity and equality issues and the ERG agrees with this.

The MS makes a case for innovation based on the novel drug class of sofosbuvir (MS p. 16) and its efficacy, safety and tolerability (MS p. 48).

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The MS reports two separate searches for clinical effectiveness information. One search was for studies of sofosbuvir (Appendix 10.2 p. 35-36) and this informs the clinical effectiveness review. The second search was for relevant (Appendix 10.4, p. 96-101) and informs a mixed treatment comparison (MTC). Apart from some minor inconsistencies, sufficient detail is given to enable the search methods for all searches (clinical, MTC, cost and HRQoL) to be reproduced.

The minimum list of databases set by NICE to be searched has been met in all instances.

In the MTC searches numerous terms were excluded from the search using the NOT operator in the search strategy. The ERG ran a search on Pubmed and confirmed that use of the NOT operator is unlikely to have caused relevant studies to be missed.

The ERG undertook searches to identify unpublished clinical trials. Four additional ongoing trials were identified (section 3.1.3).

On balance, although there are some inconsistencies, the searches reported in the MS are considered by the ERG to be fit for purpose and unlikely to have missed relevant studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

Inclusion and exclusion criteria are clearly stated in Table 8 (MS p. 53), and are consistent with the decision problem, except that any comparator is permitted. This is in contrast to the final scope (MS p. 51) which lists specific comparators. However, the MS has not included any comparators that are not in the final scope. The eligibility criteria capture all the licensed indications of sofosbuvir and the current and intended usage of sofosbuvir in the NHS (confirmed by two clinical experts). Trial phase is specified as a quality-related eligibility criterion, with phase 2 or 3 studies being considered eligible but phase 1 studies excluded. The manufacturer clarified that trial 'phase' was defined as reported by the trial authors (see NICE

Committee papers). Bias is not formally discussed at the study inclusion step, except that both blinded and open-label studies are specified as being eligible (Table 8, MS p. 53).

3.1.3 Identified studies

A flow diagram is provided for the clinical effectiveness review for studies of sofosbuvir (Fig. 3, MS p. 54). Results of searches for the MTC are not included in the flow chart (Fig 3) but are given in MS Appendix 10.4. According to the MS the MTC searches (of comparator studies) did not identify any additional sofosbuvir studies.

The MS identified 21 sofosbuvir studies from 30 publications according to the flow chart (Fig. 3, MS p.54), although the MS also states there were 36 publications (table on MS p. 55). The manufacturer clarified in response to a request from the ERG that the additional six citations refer to unpublished clinical study reports (CSRs) and protocols which provided additional information for manufacturer-sponsored studies.

Of the 21 studies identified as potentially relevant, the MS excludes eight. Four had therapies for chronic HCV outside the NICE scope. The remaining four studies excluded by the manufacturer are within the NICE scope but may have limited relevance to the NHS, or are not licensed indications for sofosbuvir. However, the MS does not provide detailed reasons for exclusion. Study GU-US-334-0114[13] was excluded as it is ongoing and full results are not yet available (MS p. 63). The MS gives no other reasons for excluding this study, although the population is atypical, being Egyptian HCV genotype 4 patients with a high frequency of schistosomiasis, and clinical experts consulted by the ERG indicated this population is not reflective of HCV genotype 4 patients seen in the NHS. The MS excludes two studies in post-liver-transplant patients (GU-US-334-0126[14] and a sofosbuvir compassionate use study[15]), stating that these are outside of the scope (MS p. 63). The ERG does not agree that these studies are outside the NICE scope, but the studies are outside of the licensed indications of sofosbuvir, according to the SmPC.[7] A dose-ranging RCT[16] was identified but not subsequently mentioned in the MS. Excluding this study would be appropriate as the sofosbuvir doses, treatment duration and timing of SVR assessments do not reflect the licensed indication.

The remaining 13 included studies are shown in Table 1. All the included RCTs meet the NICE scope and the MS inclusion criteria for at least one of their study arms. The studies are grouped

in Table 1 according to which of the licensed indications of sofosbuvir they inform, i.e. the specific combinations of HCV genotype and patients' treatment history (naive or experienced).

Table 1 Studies included in the MS grouped according to patients' HCV genotype and treatment history

Population	Trial name	Trial arms
HCV genotype 1, treatment naïve	QUANTUM (5-arm RCT, phase 2) + single cohort	1. SOF+RBV 12 weeks 2. SOF+RBV 24 weeks 3-5. *Arms excluded from MS and ERG report (drug outside scope)* 6. *Single cohort 'retreatment group' in MS but excluded from ERG report (patients had atypical treatment history on an experimental drug)*
	ATOMIC (3-arm RCT, phase 2) [a]	1. SOF+PEG+RBV 12 weeks 2. SOF+PEG+RBV 24 weeks 3. *Arm included in MS but excluded from ERG report (unlicensed SOF monotherapy)*
	SPARE (2-arm RCT, phase 2, and one non-randomised cohort) GT 1 only	1. SOF+RBV 24 weeks single cohort 2. SOF+RBV 24 weeks randomised arm 3. SOF+low-dose (600mg) RBV 24 weeks randomised arm *(technically unlicensed RBV dosing - arm included in MS and also in ERG report for supporting information, based on clinical expert advice)*
	NEUTRINO (single cohort)	1. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment naïve	FISSION (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks 2. PEG+ 800mg RBV 24 weeks
	ELECTRON (4-arm RCT, phase 2, and 4 non-randomised cohorts)	1. Randomised arm: SOF+RBV 12 weeks 2-3. *Randomised arms mentioned narratively in MS but excluded from ERG report (unlicensed durations of PEG)* 4. Randomised arm: SOF+PEG+RBV 12 weeks 5-6. *Non-randomised cohorts mentioned narratively in MS but excluded from ERG report (unlicensed SOF regimens)* 7-8. *Non-randomised cohorts excluded from MS and ERG report (unlicensed SOF regimens)*
	PROTON (3-arm RCT and single cohort)	*1-3. Randomised arms of response-guided SOF therapy excluded from MS and ERG report (unlicensed SOF regimens)* 4. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment experienced	FUSION (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks + matching placebo 4 weeks 2. SOF+RBV 16 weeks
	LONESTAR-2 (single cohort)	1. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment naive and experienced	POSITRON (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks 2. Placebo 12 weeks
	VALENCE (initially 2-arm RCT, phase 3, subsequently modified to 3-	Initial randomised design: 1. SOF+RBV 12 weeks (HCVgenotype 2/3) 2. Placebo 12 weeks (HCV genotype 2/3)

	cohort study)	Modified design: 1. SOF+RBV 12 weeks (HCV genotype 2) 2. SOF+RBV 12 weeks (HCV genotype 3) 3. SOF+RBV 24 weeks (HCV genotype 3)
HCV genotype 1/2/3 with HIV co-infection	PHOTON-1 (4 cohort study, phase 3)	1. SOF+RBV 24 weeks (HCV genotype 1, treatment naive) 2. SOF+RBV 12 weeks (HCV genotype 2, treatment naive) 3. SOF+RBV 12 weeks (HCV genotype 3, treatment naive) 4. SOF+RBV 24 weeks (HCV genotype 2/3, treatment experienced)
Any HCV genotype, pre-liver-transplant	P7977-2025 (single cohort) [a]	1. SOF+RBV 12-48 weeks

a. NB: trial does not inform the manufacturer's economic model

Study designs

Of the 13 included studies, four are phase 3 RCTs (FISSION, FUSION, POSITRON, VALENCE), four are phase 2 RCTs (QUANTUM, SPARE, ATOMIC, ELECTRON), four are non-randomised studies (NEUTRINO, LONESTAR-2, PHOTON-1, P7977-2025) and one contains both an RCT and single cohort (PROTON). Most of the data obtained from the VALENCE RCT were reported after it had been converted to a non-randomised multi-cohort study (clarified by the manufacturer on request from the ERG). Within PROTON, only the non-randomised cohort is within the licensed indication for sofosbuvir (Table 1), so only this cohort has been included in the MS and the current ERG report. The MS does not prioritise evidence from RCTs over non-randomised studies but instead gives higher priority to phase 3 than to phase 2 studies, irrespective of their design. The MS states incorrectly (p. 64) that there are no non-randomised studies. The MS also incorrectly labels the single-cohort NEUTRINO trial as an RCT and does not identify four of the phase 2 studies as being RCTs. The MS states (p. 34) that five studies are ongoing (VALENCE, ELECTRON, LONESTAR-2, PHOTON-1, P7977-2025) and mentions that for three of these studies the reported efficacy analyses are interim (VALENCE, PHOTON-1, P7977-2025).

Relevance of included studies to the decision problem

Only one head-to-head trial compared a sofosbuvir regimen directly against a relevant active comparator. The FISSION trial compared 12 weeks of SOF+RBV against 24 weeks of PEG2a+RBV in a population of mixed HCV genotype 2/3 treatment naïve patients (Table 1). Three trials (POSITRON, VALENCE, FUSION) included comparisons against placebos; however, in VALENCE (according to clarification from the manufacturer requested by the ERG),

the placebo arm was discontinued after a median duration of 8 weeks (i.e. placebo duration was shorter than that of any relevant licensed active therapy for chronic hepatitis C, so would be inappropriate as a comparator). In the FUSION trial the placebo was a short-duration addition to active treatment in one arm (SOF+RBV for 12 weeks was followed by 4 weeks of placebo). The nature of the placebos in these three trials is not reported in the MS or supporting publications but the manufacturer clarified on request from the ERG that the placebos contained no active drugs. Given the discontinuation of placebo in VALENCE and partial role of the placebo in FUSION, the ERG considers that only the POSITRON trial provided a placebo regimen that could be considered reflective of a relevant no-treatment arm (i.e., approximating best supportive care as specified in the NICE scope). As such, the head-to-head comparison of 12 weeks of SOF+RBV against the placebo in POSITRON is relevant to the decision problem.

All RCTs comparing sofosbuvir against appropriate comparators appear to have been identified and included in the clinical effectiveness section of the MS. However, RCTs that included relevant comparators without sofosbuvir were identified from a separate search and are included separately in a MTC as reported in MS Appendix 10.4. This MTC was considered not robust by the manufacturer (see section 3.1.7) and is provided in the MS appendix for information only. As can be seen in Table 1, the majority of evidence included by the manufacturer in the clinical effectiveness review is from different regimens of SOF+RBV with or without PEG2a.

Not all of the studies included in the clinical effectiveness review are fully relevant to the decision problem, since some contain specific arms or cohorts that are outside of the NICE scope and/or the marketing authorisation as specified in the SmPC.[7] Table 1 shows which arms or cohorts of these studies have been included in the MS and the current ERG report. A potential difficulty with interpreting the results of some of these studies is that they include populations with mixed HCV genotypes which are inconsistent with some of the genotype-specific licensed indications for sofosbuvir (Table 2).

Characteristics of the studies

Details of the study populations, interventions, comparators, outcomes and designs of the RCTs are fully reported in the MS (phase 3 RCTs in MS Table 9 (MS p. 57-62) and Table 10 (MS p. 65-68); phase 2 RCTs in MS Table 9 and the (non-numbered) tables on MS p. 140-143). QUOROM flow charts for the RCTs showing numbers randomised and attrition (with reasons)

are reported in the MS for the phase 3 RCTs (MS Figs 4-8, p. 91-93) but are not provided for any phase 2 RCTs. Flow charts for SPARE,[17] PROTON[18] and ATOMIC[19] RCTs are given in the primary publications cited in the MS and the ERG has referred directly to these. A flow chart for the remaining phase 2 RCT (QUANTUM) was provided by the manufacturer on request from the ERG.

Details of the study populations, interventions, comparators, outcomes and designs of the non-randomised studies are fully reported in the MS (NEUTRINO in Tables 9 & 10; other trials in Table 9 (p. 57-61) and p. 122-143). A QUOROM-type flow chart is provided in the MS only for NEUTRINO (Fig. 4, p. 91). A flow chart for PROTON is given in the primary publication[18] and the ERG has referred to directly to this; flow charts for the other phase 2 non-randomised studies were provided by the manufacturer on request from the ERG.

Table 2 HCV genotypes of the primary studies included in both the MS and ERG report

SOF indication	Trial	Regimen	GT1 %	GT2 %	GT3 %	GT4/5/6 %
HCV genotype 1, treatment naïve	QUANTUM	SOF+RBV 12 weeks [a]	76	24		
		SOF+RBV 24 weeks	76	24		
	ATOMIC	SOF+PEG2a+RBV 12 or 24 weeks	100			see footnote [e]
	SPARE	SOF+RBV 24 weeks (all arms)	100			
	NEUTRINO	SOF+PEG2a+RBV 12 weeks	89			11
HCV genotype 2/3 treatment naïve	FISSION	PEG2a+RBV 24 weeks		28	72	
		SOF+RBV 12 weeks [b]	1 [d]	27	71	
	ELECTRON	SOF+RBV 12 weeks [b]		40	60	
		SOF+PEG2a+RBV 12 weeks [c]		36	64	
	PROTON	SOF+PEG2a+RBV 12 weeks [c]		60	40	
HCV genotype 2/3 treatment experienced	FUSION	SOF+RBV 12 weeks + placebo [b]	3 [d]	35	62	
		SOF+RBV 16 weeks [b]	3 [d]	33	64	
	LONESTAR -2	SOF+PEG2a+RBV 12 weeks [c]		49	51	
HCV genotype 2/3 treatment naive and experienced	POSITRON	SOF+RBV 12 weeks [b]		53	47	
		Placebo 12 weeks		48	52	
	VALENCE	SOF+RBV 12 wk *		[redacted]		
		SOF+RBV 12 wk [b] *			[redacted]	
		SOF+RBV 24 wk			[redacted]	
HIV co-infected	PHOTON-1	SOF+RBV 24 wk, Tr naive	100			
		SOF+RBV 12 wk, Tr naive		100		

		SOF+RBV 12 wk, Tr naive [b]			100	
		SOF+RBV 24 wk, Tr experienced		100		
Pre-liver-transplant	P7977-2025	SOF+RBV 12-48 weeks or to transplant	74	13	12	2

GT: genotype, Tr: treatment
a. SOF regimen not licensed for GT1 patients (should be SOF+RBV 24 weeks or SOF+PEG2a+RBV 12 weeks)
b. SOF regimen not licensed for GT3 patients but applied to a mixed GT2/3 population
c. SOF regimen not licensed for GT2 patients but applied to a mixed GT2/3 population
d. Reported in publication[20] that GT1 not included in efficacy analysis
e. additional GT4 and GT6 patients included in safety analyses (efficacy analyses 100% GT1)
* Adverse events were pooled across genotype groups

Study populations

The main differences in patient baseline characteristics between the included studies reflect differences in the inclusion/exclusion criteria and are as would be expected according to the main study variables of interest in the submission (i.e. HCV genotype, treatment history, presence/absence of cirrhosis, presence/absence of co-infection with HIV, and eligibility for liver transplant).

The MS reports baseline characteristics in detail for the five phase 3 studies but only partial information on baseline characteristics is given in the MS for the phase 2 studies. Where necessary the ERG consulted the primary literature for missing or more precise information in four studies (ATOMIC,[19] ELECTRON,[21] SPARE,[17] PROTON[18]). In general (taking the MS and published literature together), sufficient details are available to compare baseline characteristics across the 13 included studies and across the arms/cohorts within studies, except for the QUANTUM trial which is inadequately reported both in the MS and in the publically available literature (only one short abstract is available). In their clarifications to the ERG, the manufacturer provided the ERG with the QUANTUM trial CSR.[22]

Average age of participants per trial ranged from 46 (mean, ELECTRON trial) to 59 years (median, P7977-2025 trial), with the overall age range across all relevant arms of the included studies being 19-77 years. All arms of the 13 included studies included more men than women, apart from the placebo arm of POSITRON (48% men) and the single non-randomised cohort of SPARE (40% men). Excluding these arms, the proportions of participants who were men in the remaining included arms is 55-82%. Excluding PHOTON-1 and QUANTUM which did not report quantitative data, self-reported race/ethnicity in relevant arms of the included studies was

primarily 'White' (or 'non-Black') (range 70-100%), except in the SPARE trial where 72-90% of participants in relevant arms were 'Black'. Three RCTs specifically excluded patients with cirrhosis (ATOMIC, ELECTRON, PROTON). In three further studies (QUANTUM, SPARE, P7977-2025) the number of patients with cirrhosis is not clearly reported per trial arm but according to the SmPC[7] there were only 11 cirrhotic patients in QUANTUM and SPARE combined. In the remaining seven studies the proportion of patients with cirrhosis ranged from 4% (PHOTON-1 trial) to 55% (LONESTAR-2 trial). In studies with multiple arms the within-trial difference between arms in the proportion of patients with cirrhosis did not exceed 10%.

The ERG notes that where studies provided multiple arms in the MS, the baseline characteristics of the populations did not differ substantially between arms within a study.

Outcomes

Efficacy outcomes are clearly stated for the RCTs (phase 3 in MS Table 10, p. 67; phase 2 in the (non-numbered) tables on MS p. 127-132 and p. 135-139). All eight RCTs reported SVR12 and SVR 24 apart from QUANTUM, which did not report SVR24. SVR12 was the primary outcome in the four phase 3 RCTs and QUANTUM. SVR24 was the primary outcome in SPARE and ATOMIC. No outcome was specified as primary in ELECTRON.

In addition to SVR12 and SVR24, some RCTs reported virologic responses at other times on or after treatment, as well as assessments of virologic failure, viral kinetics and/or development of HCV resistance to sofosbuvir. These additional outcomes are not specified in the NICE scope and have not been considered by the ERG (clinical advice to the ERG is that SVR12 is the key outcome influencing decisions regarding sofosbuvir-based therapy).

Efficacy outcomes in the non-randomised studies are clearly reported in the MS (p. 122-144). All four non-randomised studies reported SVR12 and SVR24 apart from the pre-liver-transplant study P7977-2025. The primary outcome was stated as SVR12 in NEUTRINO, PHOTON-1 and LONESTAR-2; safety in PROTON; and virologic response at 12 weeks after liver transplant in patients who had achieved a virologic response at their last pre-transplant visit in P7977-2025.

The MS reports that HRQoL is an 'exploratory' outcome in the four phase 3 RCTs and the phase 3 non-randomised NEUTRINO trial (see section 3.1.5). HRQoL was not assessed in the phase 2 RCTs or non-randomised studies and was not reported in any of the study publications.

Two papers reporting on HRQoL were published after the MS was submitted[23;24] and these were obtained by the ERG (one[24] was provided by the manufacturer). All the HRQoL measures reported in the MS are also reported in the papers and since the papers provide more detailed HRQoL data than the MS the ERG has assumed that the published HRQoL data[23;24] supersede those provided as 'academic in confidence' in the MS. The publications and MS do not report any HRQoL results from VALENCE. However, an unpublished conference abstract on HRQoL in the VALENCE trial was provided to the ERG by the manufacturer (2/4/2014).

Adverse events are reported in the MS for the four phase 3 RCTs and the phase 3 NEUTRINO trial but are not reported for any of the phase 2 RCTs or phase 2 non-randomised studies, although these are available for most of the phase 2 studies in the published literature.

Analysis approaches

Sample size calculations are given in the MS for all four phase 3 RCTs and for two of the four phase 2 RCTs (SPARE, ATOMIC).

[redacted] It is uncertain if SPARE was adequately powered to detect differences between arms on the SVR12 outcome, because the power calculation was based on early virologic response, not SVR12 or SVR24 (although SVR24 was stated as being the primary outcome). It is also uncertain if ATOMIC was adequately powered, because the actual difference between arms in SVR24 (0-2%) was smaller than the anticipated difference (30-25%) on which the power calculation was based. Descriptions of populations analysed, where reported in the MS, are generally consistent with descriptions in the primary publications.

Ongoing trials

The MS (p. 34) lists 11 ongoing trials whose results are likely to be available within the next 12 months – references are not given but trial summaries online are traceable from the reported titles and study numbers. The ERG has identified 4 further ongoing trials that appear relevant (GU-US-334-0119, GU-US334-0153, CCRN 2569, CCRN 968). All of these, except for CCRN 968, include some unlicensed indications and none have included HCV genotype 1 treatment experienced (high unmet need) patients.

3.1.4 Description and critique of the approach to validity assessment

The manufacturer has provided a quality assessment of the four relevant Phase 3 RCTs (FISSION, FUSION, POSITRON and VALENCE) in MS Table 20 (MS p. 95) and in MS Appendix 10.3 (p. 39-43). The quality assessment is appropriate and follows the NICE criteria. Table 3 shows the manufacturer's and ERG's independent quality assessment. As the table shows, there are some disagreements between the ERG's and the manufacturer's assessments. The ERG notes that during the VALENCE trial randomisation was broken, and the ERG considers that this has not been adequately evaluated in the manufacturer's critical appraisal. The manufacturer explained in a clarification to the ERG that during the VALENCE trial evidence from other sofosbuvir studies had suggested HCV genotype 3 patients would benefit from longer treatment duration. The VALENCE trial was therefore unblinded and genotype 3 patients were given 24 weeks of therapy instead of 12 weeks (Table 1). As a consequence of unblinding, placebo patients were discontinued after a median of 8 weeks and offered an alternative treatment protocol (the manufacturer provided no details in their clarifications about what treatment was received). The ERG therefore considers that any comparisons made against the placebo group in this trial should be interpreted with caution.

The MS does not provide quality assessments of the four relevant phase 2 RCTs (QUANTUM, ATOMIC, ELECTRON, SPARE) or the four phase 2 non-RCT studies (PROTON, LONESTAR-2, PHOTON-1 and P7977-2025). A quality assessment of the single-cohort phase 3 NEUTRINO trial is reported in the MS, but this is based on quality criteria for RCTs which do not consider potential additional biases in non-RCT studies. The manufacturer provided the missing quality assessments for the phase 2 studies to the ERG on request. Critical appraisal of the QUANTUM trial by the ERG is based on information in the trial CSR provided by the manufacturer, as only a short abstract reporting this trial was otherwise available.[25]

As shown in Table 4 the ERG's critical appraisal of the Phase 2 RCTs partly agrees with that conducted by the manufacturer. For the phase 2 non-RCT studies, the manufacturer has assessed study quality using the NICE criteria for RCTs, as they did with the phase 3 NEUTRINO trial. Given that the NICE criteria are not wholly applicable to non-RCT studies, the ERG assessed the potential risks of bias in the five non-RCT studies, drawing on the CRD's suggested criteria for prognostic factor studies.[26] In summary, the characteristics of the samples appear to be generally representative of the populations of interest in the studies, and the ERG considers that due to the nature of the SVR outcome, it is unlikely that there were any

confounding factors in these studies that might have impacted on the efficacy results. An exception is unexplained attrition in the PHOTON-1 trial in which SVR results are only presented for 28 of 40 HCV genotype 2/3 treatment experienced patients who completed treatment in the SOF+RBV 24 weeks arm [redacted] (Table 4).

Table 3 Manufacturer and ERG assessment of trial quality of the Phase 3 RCTs

		FISSION	FUSION	POSITRON	VALENCE
1. Was randomisation carried out appropriately?	MS:	Yes	Yes	Yes	Yes
	ERG:	Unclear	Yes	Unclear	Yes
Comment: FISSION trial: patients were randomised using a centralised allocation system, but no details are provided about how the random sequence was generated. FUSION and VALENCE trials: Patients were randomised using an Interactive Web Response System (although, note, that randomisation was later broken in the VALENCE trial due to unplanned modifications to patients' treatment). POSITRON trial: no information provided about how the randomisation sequence was generated.					
2. Was concealment of treatment allocation adequate?	MS:	N/A	Yes	Yes	Yes
	ERG:	Yes	Yes	Unclear	Yes
Comment: FISSION, FUSION and VALENCE trials: a centralised allocation system was used. Note: the manufacturer has marked this criterion as 'N/A' for the FISSION trial as it was an open-label study. However, this criterion relates to whether or not treatment allocation could be foreseen prior to randomisation rather than blinding. POSITRON trial: no information provided about how allocation was concealed.					
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	Yes
Comment:					
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	N/A	Yes	Yes	Yes
	ERG:	No	Yes	Yes	No
Comment: FISSION trial: open-label study. FUSION and POSITRON trials: Patients, clinicians, the investigator and sponsors blinded to treatment. VALENCE trial: manufacturer clarified to the ERG that the trial was unblinded.					
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	No	No	No	No
	ERG:	No	No	No	Yes
Comment: VALENCE trial: 81 patients assigned to the placebo arm discontinued the study, 79 of which were terminated by the sponsor (see Figure 8, MS p. 93), compared to 3–4 patients discontinuing in the genotype 3 SOF+RBV 12 and genotype 3 SOF+RBV 24 arms. The placebo patients were then offered an unspecified alternative treatment regimen. Results for the placebo arm are not reported in the MS or trial publication, except for adverse events.					
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	No	No
	ERG:	No	No	No	Yes
Comment: VALENCE trial: HRQoL was measured in the trial, but results for this outcome are not reported in the MS or related trial publication.[27]					
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	No

to account for missing data?					
Comment: FISSION, FUSION and POSITRON trials: the primary outcomes were analysed in the full analysis set (FAS), defined as patients who had received at least one dose of the study drug in the FISSION and FUSION trials (FAS population was not defined in the POSITRON trial but the manufacturer clarified to the ERG that the FAS population consisted of all randomised patients who received at least one dose of the study drug). In the FUSION trial, however, the number of patients included in the SVR12 outcome analysis results reported in the MS is smaller than the number receiving at least one dose of the study drug. Although none of the trials used a true ITT analysis, the discrepancies between the number of patients randomised and those included in the SVR12 outcome analyses are small and unlikely to impact outcomes. VALENCE trial: ITT analyses were not conducted; randomisation was broken (see section 3.1.4).					

Table 4 Manufacturer and ERG assessment of trial quality of the Phase 2 RCTs

		ATOMIC	ELECTRON	SPARE	QUANTUM
1. Was randomisation carried out appropriately?	MS:	Yes	Yes	Yes	Yes (for Groups C[a] and G[b])
	ERG:	Yes	Unclear	Unclear	Unclear
Comment: ATOMIC trial: randomisation was performed using a computer-generated randomisation sequence and an interactive web-based response system. ELECTRON trial: randomisation method not described. SPARE trial: unclear how the random sequence was generated (only stated that a set of 60 random numbers was used). QUANTUM trial: method of randomisation unclear.					
2. Was concealment of treatment allocation adequate?	MS:	NA	NA	NA	NA
	ERG:	Yes	Unclear	No	Unclear
Comment: randomisation was performed centrally using an interactive web-based response system. ELECTRON trial: method used to conceal treatment allocation not described. SPARE: block randomisation was used and it is possible that treatment allocation could be foreseen prior to randomisation. QUANTUM trial: no details provided.					
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	No
Comment: QUANTUM trial: proportionally more patients in the SOF + RBV for 12 weeks arm than the SOF + RBV for 24 weeks arm had a HCV RNA (log10 IU/mL) of < 6 (36% vs 16%)					
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	NA	NA	NA	NA
	ERG:	No	No	No	Yes
Comment: ATOMIC trial: open-label study. The investigators considered that blinding was not feasible due to the inconvenience it would cause patients as they would have to be given placebo injections. Patients, investigators and study personnel administering the treatment were not blinded to treatment allocation at any point during the study. ELECTRON trial: open-label trial. SPARE blinding not reported in MS but publication [17] states open label.					
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	No	No	No	No
	ERG:	No	No	No	No
Comment: ATOMIC trial: proportionally more patients treated with SOF+PEG2a+RBV for 24 weeks discontinued treatment than those treated with SOF+PEG2a+RBV for 12 weeks (22% compared with 10%). However, similar proportions of patients in each arm completed follow-up (90%, 92%), so this will not have affected the results of the trial (ATOMIC analysis population in Table 2 of the publication[19] suggests analysis for SVR included all randomised patients). SPARE trial difference between randomised and analyses populations was small (n=1, n=3) according to publication.[17]					
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	No	No
	ERG:	No	No	No	No

Comment:					
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	MS:	Yes	Yes	Yes	Yes
	ERG:	Unclear	Yes	Yes	Yes
Comment: ATOMIC trial: Analyses were conducted in the ITT population, defined as all randomised patients who received at least one dose of the study drug. However, it is unclear how missing data were imputed. ELECTRON trial: all patients enrolled were followed up. SPARE trial: ITT analyses were used and missing data were imputed appropriately. QUANTUM trial: the efficacy analysis set consisted of all patients who received at least one dose of the study drug and the ERG notes that all randomised patients were included in the analyses.					

[a]Sofosbuvir 400 mg and RBV 1200 mg or 1000 mg for 12 weeks
[b]Sofosbuvir 400 mg and RBV 1200 mg or 1000 mg for 24 weeks

3.1.5 Description and critique of manufacturer's outcome selection

The outcomes selected by the manufacturer are appropriate and reflect the NICE scope. Mortality was specified in the scope but this is not an explicitly reported outcome in the MS; however it can be deduced from the presented flow charts and cited publications.

Adverse events are reported appropriately by the MS for the phase 3 studies. Several phase 2 studies also reported adverse events but these are not considered in the MS (the ERG has consulted both the phase 2 and 3 studies when considering adverse events – see section 3.3).

The manufacturer's measures of HRQoL (SF-36; CLDQ-HCV; FACIT-F; WPAI) seem appropriate as they cover 5 key concepts identified as important to patients on therapy for chronic hepatitis C (depression/anxiety, fatigue, flu-like symptoms, cognitive function, insomnia[28]). However, it should be noted that none of the sofosbuvir studies employed the EQ-5D which is the preferred instrument for developing utility estimates in health economic evaluations for NICE.[29]

3.1.6 Description and critique of the manufacturer's approach to trial statistics

Analyses for three of the studies reported in the MS are specified as being 'interim' or 'ongoing' (VALENCE, PHOTON-1 and P7977-2025). The MS explains how the SVR outcome in the studies was statistically analysed and the ERG considers the methods employed were appropriate (group differences were not formally tested statistically in the ELECTRON trial). Comparisons of SVR rates between arms in the POSITRON and VALENCE studies were stratified by presence/absence of cirrhosis. Pre-specified subgroup analyses of SVR12 by demographic and baseline characteristics (age, gender, race, ethnicity, cirrhosis status,

genotype, HCV RNA level, BMI, alanine aminotransferase (ALT) level, and IL28B genotype) were conducted in the phase 3 studies, although no indication of the statistical power of any subgroup analyses is given in the MS. Subgroup analyses were also conducted according to response to previous HCV treatment in FUSION and patients' suitability for interferon in POSITRON. Subgroup analyses specified in the NICE scope or informing the economic model are considered by the ERG in section 3.3.

Full ITT[30] analyses appear to have been conducted in the phase 2 SPARE and ELECTRON and QUANTUM RCTs (Table 4) (ELECTRON and QUANTUM did not explicitly mention ITT analysis but the outcomes were reported for all randomised patients). In the remaining RCTs strict ITT analyses were not conducted but the ERG considers the analyses to be acceptable because there are only small differences between the numbers of patients randomised and analysed, and conservative methods were used to impute missing data (see Table 3 and Table 4). An exception is the phase 3 VALENCE trial, in which randomisation was broken and therefore the analyses were not conducted in the ITT population. It remains unclear from the MS and trial publication why 11 genotype 3 patients in the VALENCE trial were not switched from 12 weeks of SOF+RBV therapy to 24 weeks (which was the therapy given to the other genotype 3 patients).

For HRQoL outcomes, which were assessed in NEUTRINO, FISSION, FUSION, POSITRON and VALENCE, the MS mentions that analyses were 'exploratory', although the ERG has assumed (section 3.1.3) that two new publications[23;24] reporting HRQoL results in NEUTRINO, FISSION, FUSION and POSITRON supersede the exploratory analyses reported in the MS. There are some uncertainties about the analyses of HRQoL, however, as sample sizes reported in the publication on SF-36 results[24] imply that in three of these four studies all the randomised patients received HRQoL questionnaires, but for the FISSION trial HRQoL results were reported for 40-42% of the numbers randomised per arm. Summary results of the HRQoL analyses in VALENCE were provided by the manufacturer to the ERG (2/4/2014) in the form of an unpublished abstract which does not report the number of patients analysed.[31].
The MS reports all relevant trial results for the SVR, adverse events and HRQoL outcomes from the Phase 3 studies, except for the HRQoL outcome in the VALENCE trial.

Patient numbers were provided for most of the analyses, except for some of the subgroup analyses (i.e. SVR by cirrhosis status in NEUTRINO, and subgroup categories in MS Figures

10, 11, 15, 17), which means that these analyses should be interpreted with caution because it is unclear if they were adequately powered to detect differences between subgroups.

In summary, the manufacturer's approach to trial statistics is generally appropriate. Results for subgroup analyses should be interpreted with caution as sample sizes were often small. The ERG considers that SVR12 for HCV genotype 3 patients receiving 24 weeks of therapy in the VALENCE trial should be interpreted with caution as it is unclear why 11 patients are missing. HRQoL results from the FISSION trial should also be interpreted with caution as they are reported for an unexplained subgroup of the randomised trial population. It should be noted, however, that the initial trial designs and statistical approaches employed are not all directly relevant to the outcomes that inform the economic model since the model inputs for SVR are taken from HCV genotype-specific and cirrhosis/non-cirrhosis subgroups in some of the studies.

3.1.7 Description and critique of the manufacturer's approach to the evidence synthesis

A narrative review of the evidence is provided in the MS. The manufacturer did not conduct a meta-analysis and the ERG considers this decision to be appropriate, given that most of the studies focus on comparing different sofosbuvir combination treatments for different treatment durations and the studies varied in the patient populations studied according to HCV genotype infection and treatment experience. Trials of comparators are considered in the MTC (see below) and the cost effectiveness assessment section.

The narrative review and the tabulated data in the MS generally reflect the data in the publications of the Phase 3 FISSION,[20] FUSION,[32] and POSITRON[32] trials. There is a minor error in the adverse event table for POSITRON (Table 35, MS p. 153), where data for mean treatment duration have been transposed into the wrong column, but this does not affect the interpretation of the results. The manufacturer states on MS p. 154 that the side effect profile of sofosbuvir is similar to placebo, and the ERG agrees that data from the POSITRON trial (the only trial to include a true placebo arm) indicate that on the whole this is the case, but that rates of fatigue, insomnia and anaemia were much higher amongst patients treated with sofosbuvir than with placebo (difference 20%, 15% and 13% respectively). The ERG could not check the HRQoL data reported in the MS or data from the VALENCE or QUANTUM studies as these were not reported in either the trial publications or the CSRs, which were supplied by the

manufacturer to the ERG in their clarifications. The Phase 2 RCTs and the non-RCT studies data presented in the MS accurately reflect the data in the original publications.

Mixed Treatment Comparison

The manufacturer conducted a MTC to explore the comparative data for sofosbuvir versus other relevant comparators (MS section 6.7, page 154). The MTC was conducted for treatment naive IFN eligible patients with GT1, GT2 or GT3 infection, but was not feasible in the other genotype groups due to absence of data.

The MS stated that the MTC results were not robust and therefore they did not populate the economic base case with efficacy data from the MTC. The ERG has completed a checklist for the key issues of the MTC for homogeneity, similarity and consistency (Table 5).

The MTC considered homogeneity with respect to design, patient characteristics and outcomes and selected studies according to specific eligibility criteria, as described in MS Appendix 4, page 54. Between-study heterogeneity was tested using the chi-squared test and the inconsistency index (I^2).

Table 5 MTC checklist

Checklist		Response (yes/no)
Does the MS present an MTC?		Yes
Are the MTC results used to support the evidence for the clinical effectiveness of the intervention		No
Are the MTC results used to support the evidence for the cost-effectiveness of the intervention		No
Homogeneity		
	1. Is homogeneity considered?	Yes
	2. Are the studies homogenous in terms of patient characteristics and study design?	Yes
	3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Yes
	4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. subgroup analysis, sensitivity analysis, meta-regression)	N/A
Similarity		
	1. Is the assumption of similarity stated?	Yes
	2. Have they justified their assumption?	Yes
Consistency		
	1. Does the analysis explicitly assess consistency?	Yes
	2. Does the method described include a description of the analyses/	Yes

	models/ handling of potential bias/ inconsistency/ analysis framework?	
	3. Are patient or trial characteristics compared between direct and indirect evidence trials?	No
	4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	N/A

N/A: Not applicable

For HCV genotype 1 treatment naive IFN eligible patients, included studies had generally similar patient characteristics; however, they differed by the proportion of patients with cirrhosis (MS Appendix 4, Table 8). These differences in cirrhosis were taken into consideration in sensitivity analyses. For HCV genotype 2/3 treatment naive IFN eligible patients, included studies had similar patient characteristics; however, cirrhosis status was not available for all studies and the definition of cirrhosis varies according to the scoring measure used.

The MTC included 20 studies on HCV genotype 1, including two sofosbuvir RCTs (PROTON and ATOMIC), four telaprevir trials, two boceprevir trials and 12 PEG trials. The results for the MTC for patients with HCV genotype 1 are given in Table 14 of MS Appendix 10.4 (p. 80). The results estimate a SVR for sofosbuvir of 81.99% compared to SVR for PEG2a+RBV of 46.25%. Twelve trials on HCV genotype 2/3 were included in MTC, including one sofosbuvir RCT (FISSION) and 11 PEG trials. The results estimate SVR of 77.85% for sofosbuvir and 77.58% for PEG2a+RBV. In the base case, the MTC differentiated between studies that used weight-based doses and flat doses of ribavirin, and then provided subgroup analyses without differentiating between the flat and weight based dosing.

The MS reports several limitations to the MTC and concludes that the results from the MTC could not be considered robust. Due to the absence of data an MTC network could not be formed for all the relevant populations and an MTC was only conducted for treatment naive IFN eligible patients with HCV genotype 1, 2 and 3 infection. The MS economic model required that efficacy data were split out by cirrhotic and non-cirrhotic status and these data were not available for all trials. In HCV genotype 1 patients, a network including sofosbuvir was only possible by linking two small phase 2 trials (ATOMIC and PROTON) which only included non-cirrhotic patients. In HCV genotype 2 and 3 patients, the MTC results were based on genotypes 2 and 3 combined for cirrhotic and non-cirrhotic patients combined.

The ERG considers the justification for not using the MTC results in the economic model to be reasonable. For HCV genotype 1 treatment naive interferon eligible patients, results are unlikely

to be robust in the MTC by using two studies with no cirrhotic patients that had small numbers of patients; in particular the PROTON study has only 26 patients with PEG2a treatment. For HCV genotype 2 and 3 patients, the MTC may be considered not robust enough to use for the economic model, largely due to the manufacturer's choice to structure the model by cirrhotic and non-cirrhotic patients and separately for genotype 2 and 3 patients, although other appraisals have used alternative model structures and presented results for HCV genotypes 2 and 3 together.

3.2 Summary statement of manufacturer's approach

The manufacturer's approach to the clinical effectiveness review was assessed by the ERG using CRD quality assessment criteria (Table 6). The systematic review carried out by the MS is of generally good quality according to the CRD criteria, apart from the lack of assessment of the quality of phase 2 studies (both RCT and non-RCT) although this was provided in clarifications from the manufacturer (see NICE Committee papers). The MS reports that inclusion/exclusion screening and data extraction were conducted independently by two reviewers, but does not specify how many reviewers assessed study quality.

Table 6 Quality assessment (CRD criteria) of MS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes, on the whole. There were some minor inconsistencies in search strategies but on balance the searches were considered to be reasonably comprehensive and reproducible, although no details were provided relating to searches of company databases (Appendix 10.12.6; p. 289) and searches for conference abstracts were limited mainly to two series of European and American conference proceedings.
3. Is the validity of included studies adequately assessed?	No. Assessment of the quality of the phase 2 RCTs or non-randomised studies was not provided (Appendix 10.7, p. 120) (manufacturer subsequently provided this see section 3.1.4). No narrative discussion is presented and it is not specified how many reviewers conducted the quality assessment.
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

The submitted evidence does not fully meet the decision problem defined in the MS (p. 51) for several reasons:

- There is only one fully relevant head-to-head trial of a comparator specified in the NICE scope (PEG2a+RBV 24 weeks in the FISSION trial on HCV genotype 2/3).
- There is only one RCT that tested sofosbuvir head-to-head against a relevant duration of inactive placebo (12 weeks of SOF+RBV compared to 12 weeks of placebo in the POSITRON trial on HCV genotype 2/3); the placebo might arguably reflect best supportive care (i.e. no treatment) and as such would be a relevant to the decision problem, assuming placebo effects are considered negligible or conservative.
- Evidence for comparators is limited: it was not possible to construct a robust MTC of sofosbuvir and comparators due to a shortage of relevant studies for the licensed indications of the therapies.

3.3 Summary of submitted evidence

Results for SVR

The MS presents virologic response data for various on-treatment and post-treatment timepoints within the phase 2 and phase 3 studies. The ERG has focused on SVR at 12 weeks after the end of treatment (i.e. SVR12) as this is the virologic outcome of main clinical interest and treatment decisions are generally not based on on-treatment virologic responses when patients are treated with sofosbuvir. As some studies did not report SVR12, SVR at 24 weeks after end of treatment (i.e. SVR24) is also presented.

The SVR12 outcomes are summarised below according to the patients' HCV genotypes and treatment history (some studies reported mixed HCV genotype populations, as indicated in the Tables below).

HCV genotype 1, treatment naive

No head-to-head intervention/comparator studies are available for this indication, meaning that the SVR data are all from different sofosbuvir regimens. These are SOF+RBV or SOF+PEG2a+RBV taken for 12 or 24 weeks. The SVR data for this indication are from the RCTs ATOMIC, QUANTUM and SPARE and the single-cohort NEUTRINO study (Table 7). A single-cohort trial (PHOTON-1) on a pre-specified subgroup of HCV genotype 1 patients with HIV co-infection is included in the MS and is considered separately below (section 'Subgroup analyses: results for subgroups specified in the NICE scope'). It should be noted that

QUANTUM had a mixed 1/2/3/4 HCV genotype population in which 76% of patients had genotype 1 and 24% had genotype 2 or 3. NEUTRINO was a mixed 1/4/6 HCV genotype study in which 89% of patients had HCV genotype 1 and the remaining 11% had genotypes 4-6. Populations in the SPARE and ATOMIC RCTs had 100% HCV genotype 1.

Table 7 Virologic responses: HCV genotype 1, treatment naïve

Trial and HCV genotype (GT)	Intervention	Sample size	SVR12, n/N (%; 95% CI) [c]	SVR24, n/N (%; 95% CI)
ATOMIC (from MS & Kowdley et al[19]) GT 1 only	SOF+PEG2a +RBV 12 weeks	N=52	ITT: 47/52 (90; 79-97%)	ITT: 46/52 (89; 77-96) PP: 46/48 (96; 86-100)
	SOF+PEG2a +RBV 24 weeks	N=109	ITT: 101/109 (93; 86-97)	ITT: 97/109 (89; 82-94) PP: 97/99 (98; 93-100)
QUANTUM (from MS & Lalezari et al[25]) GT 1/2/3	SOF+RBV 12 weeks	N=25 GT1: 76% [a] GT2/3: 24% [a]	[redacted] [d]	Not reported
	SOF+RBV 24 weeks	N=25 GT1: 76% [a] GT2/3: 24% [a]	[redacted] [d]	Not reported
SPARE (from MS & Osinusi et al[17]) GT 1 only	SOF+RBV 24 weeks	N=10 (non-randomised single cohort) [b]	ITT: 9/10 (90; 55-100) PP: 9/9 (100; 66-100)	Same as SVR12 (both PP and ITT analyses)
	SOF+RBV 24 weeks	N=25 (randomised arm)	ITT: 17/25 (68; 46-85) PP: 17/24 (71; 49-87)	Same as SVR12 (both PP and ITT analyses)
	SOF+ low-dose (600 mg/day) RBV 24 weeks	N=25 (randomised arm)	ITT: 12/25 (48; 28-69) PP: 12/22 (55; 32-76)	Same as SVR12 (both PP and ITT analyses)
NEUTRINO (from MS & Lawitz et al[20]) GT 1/4/5/6	SOF+PEG2a +RBV 12 weeks	N=327 GT1: 89% (n=291) GT4: 9% (n=28) GT5: <1% (n=1) GT6: 2% (n=6)	295/327 (90; 87-93) 296/327 (91) [e] GT1: 90 [f] GT 4/5/6: 97 [f]	(91; not reported)

ITT: intention to treat population; PP: per protocol population

a. HCV genotype proportions are not reported separately by arm in the MS or publication – ERG has assumed the proportions of GT 1/2/3 would be the same for each arm since allocation was random

b. SVR data from publication[17] supplementary appendix (not reported in MS)
c. None of the studies reported SVR12 by HCV genotype subgroup
[redacted]
e. A revised SVR12 rate of 91% (296/327) was calculated following the addition of one GT1 patient who was <LLOQ at SVR4, was "lost to follow-up = failure" at SVR12, but was subsequently "found" and achieved SVR24. SVR12 was back extrapolated from SVR24 for this patient.
f. from the SmPC[7]

[redacted]For the SOF+RBV 12-week regimen, SVR12 rate is only available from the QUANTUM trial and was [redacted].

For the SOF+RBV 24-week regimen, SVR12 rate [redacted] in QUANTUM to 68% (95% CI 46-85%; N=25) in the randomised arm of the SPARE trial. A single non-randomised 'proof of concept' cohort (N=10) within the SPARE trial achieved SVR12 of 90% (95% CI 55-100%) (95% CI not reported in the MS - obtained from the publication[17]).

For the SOF+PEG2a +RBV 12-week regimen, SVR12 was 90% in both the NEUTRINO cohort (95% CI 87%-93%) and a randomised arm of the ATOMIC trial (95% 79-97%; N=52).

For the SOF+PEG2a +RBV 24-week regimen, SVR12 rate is only available from a randomised arm of the ATOMIC trial and is reported as 93% (95% CI 86-97; N=109).

SVR24 rates are not available for QUANTUM or the NEUTRINO study. In the ATOMIC trial SVR24 was the primary outcome. Based on the ITT population (all patients who were enrolled and received at least one dose of study drug), SVR24 rates in the ATOMIC trial were slightly lower than SVR12 rates, although the publication[19] does not give a clear explanation.

HCV genotype 1 treatment experienced

No studies of sofosbuvir providing any virologic response rates were identified for this indication.

HCV genotype 2/3, treatment naive

SVR12 data are available from one phase 3 RCT (FISSION), a phase 2 RCT (ELECTRON), and a single cohort of a phase-2 trial (PROTON) (Table 8). These studies all had populations with mixed HCV genotype 2 and 3 (FISSION included a single genotype 1 patient who was excluded from efficacy analyses). The FISSION trial had mostly genotype 3 patients (71-72%

per arm) whilst ELECTRON had slightly more genotype 3 patients (60-64% per arm) than genotype 2 and PROTON had slightly more genotype 2 patients (60%) than genotype 3.

Table 8 Virologic responses: HCV genotype 2/3, treatment naïve

Trial and HCV genotype (GT)	Intervention	Sample size	SVR12, n/N (%; 95% CI)	SVR24, n/N (%; 95% CI)
FISSION (from MS & Lawitz et al[20]) GT 1/2/3 [a]	PEG2a +RBV 24 weeks	N=243 GT2: 28% (n=67) GT3: 72% (n=176)	162/243 (67) [b] SVR% by genotype: GT2: 78 GT3: 63	65%
	SOF+RBV 12 weeks	N=253 GT1: 1% (n=1) GT2: 27% (n=70) GT3: 71% (n=183)	170/253 (67) [b] SVR% by genotype: GT2: 97 [c] GT3: 56	67%
ELECTRON (from MS & Gane et al[21]) GT 2/3	SOF+RBV 12 weeks	N=10 GT2: 40% (n=4) GT3: 60% (n=6)	10/10 (100; 69-100) [d] SVR(%) by genotype: GT2: 4/4 (100) GT3: 6/6 (100)	Same as SVR12
	SOF+PEG2a +RBV 12 weeks	N=11 GT2: 36% (n=4) GT3 64% (n=7)	11/11 (100; 72-100) [d] SVR(%) by genotype: GT2: 4/4 (100) GT3: 7/7 (100)	Same as SVR12
PROTON (from MS & Lawitz et al[18]) GT 2/3	SOF+PEG2a +RBV 12 weeks	N=25 G2: 60% (n=15) G3: 40% (n=10)	23/25 (92; 74-99) SVR% by genotype: GT2: 93 GT3: 90	Same as SVR12 [e]

a. One HCV genotype 1 patient was present but their results were not included in efficacy analysis
b. SOF+RBV shown to be non-inferior to PEG2a +RBV; absolute difference in SVR12 after adjusting for stratification factors 0.3% (95% CI -7.5 to 8.0) in favour of SOF+RBV.
c. reported as 95% (69/73) in the SmPC[7]
d. 95% CI from publication[21] (not reported in MS)
e. One patient who achieved SVR12 had missing values for post-treatment week 24; excluding this patient from the denominator resulted in 42/46 patients (91%) (95% CI 79-98%) achieving SVR24

A head-to-head comparison of 12 weeks of SOF+RBV (N=256; N = 253 in analysis) against 24 weeks of PEG2a +RBV (N=243) was made in the FISSION trial. Both groups achieved an SVR12 of 67% (95% CI values not reported). The absolute difference between treatment groups after adjustment for stratification was 0.3% (95% CI -7.5 to 8.0%); non-inferiority p<0.0001).

The SOF+RBV 12-week regimen was also provided in a randomised arm of the ELECTRON trial and the reported SVR12 is 100% (95% CI 69-100%), although it should be noted that sample size was relatively small (N=10).

The SOF+PEG2a +RBV 12-week regimen was provided in one arm each from the ELECTRON trial PROTON study, although these studies, especially ELECTRON, had relatively small sample sizes. The SVR12 rates were, respectively 100% (95% CI 72-100%; N=11) and 92% (95% CI 74-79%; N=25) (95% CIs for each trial not provided in the MS – obtained from the study publications[18;21]).

SVR24 rates in these three studies were identical to the SVR12 rates reported above except for the PEG2a +RBV arm of the FISSION trial, in which SVR24 was reported as 65% as compared to the SVR12 of 67%.

HCV genotype 2/3, combined treatment experienced and treatment naive
SVR12 rates for this indication are available from POSITRON RCT and the VALENCE study (Table 9). It should be noted that VALENCE started out as an RCT combining HCV genotype 2 and 3 patients but randomisation was subsequently broken to create three cohorts, to enable HCV genotype 3 patients to be treated for a longer duration (i.e. 24 weeks). These studies compared the SOF+RBV 12-week regimen against either an inactive placebo (POSITRON) or against SOF+RBV 24-week therapy (VALENCE). The POSITRON RCT reports outcomes for a mixed HCV genotype population contained roughly equal numbers of patients with genotype 2 (48-53% per arm) and genotype 3 (47-52% per arm); in the VALENCE study SVR12 data are reported separately for patients with HCV genotypes 2 and 3.

The SOF+RBV 12-week regimen resulted in SVR12 rates of 78% (95% CI 72-83%; N=207) in mixed genotype 2/3 patients (POSITRON), [redacted]) genotype 2 patients (VALENCE) and [redacted]) in genotype 3 patients (VALENCE), although it should be noted that the sample size for genotype 3 was relatively small.

The SOF+RBV 24-week regimen given to genotype 3 patients in the VALENCE trial resulted in an SVR rate of [redacted]).

In the POSITRON trial, SVR12 was recorded in the inactive placebo arm as 0%, consistent with the lack of any spontaneous disappearance of HCV RNA. SVR24 rates in POSITRON were the same as for SVR12; data on SVR24 have yet to be reported in the ongoing VALENCE trial.

Table 9 Virologic responses: HCV genotype 2/3, combined treatment experienced and treatment naïve

Trial and HCV genotype (GT)	Intervention	Sample size	SVR12, n/N (%; 95% CI)	SVR24 (%)
POSITRON (from MS & Jacobson et al[32]) GT 2/3	SOF+RBV 12 weeks	N=207 GT2: 53% (n=109) GT3: 47% (n=98)	161/207 (78; 72-83) [a] SVR% by genotype: G2: 93 G3: 61	78
	Placebo 12 weeks	N=71 GT2: 48% (n=34) GT3: 52% (n=37)	0/68 (0) [b]	0
VALENCE (from MS and Zeuzem et al[27]) GT 2/3	[redacted]	[redacted](n=73) (n=11) (n=250)	[redacted] [c]	[redacted]

a. 95% CI from publication[32] (not reported in MS)
b. HCV RNA results unavailable for 3 patients
[redacted]

HCV genotype 2/3, treatment experienced

SVR12 rates are available for this indication for three different regimens, from two arms of the phase 3 FUSION RCT and from the single-cohort LONESTAR-2 study (Table 10). The FUSION trial contained slightly more patients with HCV genotype 3 (62-64% per arm) than genotype 2 (33-55% per arm) and reported SVR12 for the mixed genotype population and separately for each genotype. In the LONESTAR-2 cohort the proportions of genotypes 2 and 3 were similar (49 and 51% respectively) and SVR rates were reported both for the mixed genotype population and separately for each genotype.

The FUSION RCT compared SOF+RBV for 12 weeks followed by 4 weeks of a matching placebo against SOF+RBV for 16 weeks. SVR12 rate was 50% (95% CI 40-60%; N=100) in the 12-week-plus-placebo group and 73% (95% CI 63-81%; N=95) in the 16-week therapy group. These SVR12 rates were statistically superior to an historic 'control' rate of 25%.

The LONESTAR-2 study provided SOF+PEG2a +RBV to a single cohort for 12 weeks, achieving an overall SVR12 rate for genotype 2/3 patients of 89% (95% CI not reported; N=47). SVR12 rates for HCV genotype 2 (n=23) and genotype 3 (n=24) were, respectively, 96% and 83% (95% CIs not reported). SVR24 rates were not reported in these studies.

Table 10 Virologic responses: HCV genotype 2/3, treatment experienced

Trial and HCV genotype (GT)	Intervention	Sample size	SVR12, n/N (%; 95% CI)
FUSION (from MS & Jacobson et al[32]) [a] GT 1/2/3	SOF+RBV 12 weeks (+ 4 weeks matching placebo)	N=103 GT1: 3% (n=3) [b] GT2: 35% (n=36) GT3: 62% (n=64)	50/100 (50; 40-60) [c] SVR% by genotype: GT2: 86% [d] GT3: 30%
	SOF+RBV 16 weeks	N=98 GT1: 3% (n=3) [b] GT2: 33% (n=32) GT3: 64% (n=63)	69/95 (73; 63-81) [c] SVR% by genotype: GT2 : 94 [e] GT3 : 62
LONESTAR-2 (from MS & Lawitz et al[33]) GT 2/3	SOF+PEG2a +RBV 12 weeks	47 (FAS population) GT2: 49% (n=23) GT3: 51% (n=24)	42/47 (89) SVR(%) by genotype: GT2: 22/23 (96) GT3: 20/24 (83)

a. Difference in SVR12 between therapy duration groups:
Overall: -23% (95% CI -35 to -11%); p<0.001
GT2: -8% (95% CI -24 to 9%)
GT3: -32% (95% CI -48 to -15%)
b. HCV genotype 1 patients were not included in efficacy analyses
c. HCV RNA results are unavailable for 3 patients in each group; according to the MS (footnote, p. 108) this appears to represent 6 patients who had recombinant GT2/1 HCV infection and were excluded. In the SmPC[7] the 16-week therapy group has a slightly lower SVR12 (71%) than reported in the MS (73%) due to inclusion of these 6 patients in the original analysis.
d. reported as 82% (32/39) in the SmPC[7]
e. reported as 89% (31/35) in the SmPC[7]

HCV genotypes 4/5/6, treatment naive

No studies of sofosbuvir providing any virologic response rates were identified for this indication except for studies primarily on genotype 1 patients which contained a minority of genotype 4/5/6 patients. Clinical expert opinion is that SVR rates in genotype 4/5/6 treatment naive patients would be comparable with those of genotype 1 treatment naive patients (Table 7).

Mortality

Mortality occurred in four of the 13 included studies, although this is not explicitly mentioned in the MS.

In the FISSION trial, the MS reports two patients (<1%) died in the 12-week SOF+RBV group, one during treatment and the other after completion of treatment. One patient (<1%) also died in the FISSION trial after completion of the 12-week PEG2a+RBV comparator therapy. The causes of mortality were not reported in the MS or cited literature.

In the POSITRON trial the MS reports one death (<1%) occurred in the 12-week SOF+RBV group. Cause of mortality was not stated, although the supplementary appendix to the primary publication[32] stated that no treatment-emergent deaths occurred.

In the PHOTON-1 trial, which focused on HIV co-infected patients, one death (<1%) occurred after completion of the 12-week SOF+RBV therapy and the cause of mortality (suicide) was considered not directly related to treatment (reported in a presentation,[34] not in the MS).
In the P7977-2025 trial, which was on patients awaiting liver transplant and receiving 12-48 weeks of SOF+RBV, five deaths occurred during the reporting period, of which 2 (3%) were pre-transplant and 3 (5%) occurred post-transplant (reported in a presentation,[35] not in the MS). Causes of mortality were not reported.

Results for Health related quality of life

The MS presents only exploratory analyses of HRQoL in four RCTs (FISSION, FUSION, POSITRON, NEUTRINO) (section 3.1.5) and the ERG assumes (section 3.1.3) that these have been superseded by published HRQoL analyses which became available after the MS was submitted.[23;24] The ERG has summarised here, as supporting information, the key HRQoL results reported in the manufacturer's two recent publications,[23;24] and these are broadly consistent with the preliminary HRQoL results from the exploratory analyses presented in the MS. No HRQoL results for VALENCE are given in the MS, but an unpublished abstract giving some HRQoL results from this trial[31] are considered below.

General HRQoL, assessed using the SF-36 in the FISSION, FUSION and POSITRON RCTs and the NEUTRINO trial,[24] decreased during therapy in all treatment arms except in the SOF+RBV arm of FISSION where an on-treatment increase was observed. Effects of sofosbuvir

therapy on SF-36 scores were transient in all the studies with a return to baseline scores by the end of follow up. In POSITRON, HRQoL of patients receiving 12 weeks of SOF+RBV was not impaired compared to the inactive placebo arm. HRQoL was significantly more impaired during 24 weeks of PEG2a+RBV than during 12 weeks of SOF+RBV in FISSION, but the duration of SOF+RBV therapy (12 or 16 weeks) in FUSION made no obvious difference to HRQoL. The authors concluded that treatment-related impairment of HRQoL during SOF+RBV therapy is 'moderate' but does not increase with longer treatment duration. Limitations of the evidence are that no comparisons were made of 12 weeks against 24 weeks of SOF+RBV and, as mentioned above (section 3.1.6), there are some uncertainties around the sample sizes involved in the FISSION trial HRQoL analyses.

Patients' disease-specific HRQoL, fatigue-related functional ability, and work productivity were assessed in the FUSION and NEUTRINO studies using the CLDQ-HCV, FACIT-F and WPAI instruments respectively.[23] These instruments capture abdominal and systemic symptoms, fatigue, emotional function, worry, and activity; questions about depression and irritability);[36] physical, social/family, emotional and functional aspects of well-being and other concerns including fatigue;[37] and issues around work absenteeism and work productivity loss.[38] In FUSION, both the 12 and 16-week durations of SOF+RBV negatively affected disease-specific HRQoL, fatigue levels and work productivity but effects were transient and scores had returned to baseline (or better) by 4 weeks after the end of treatment. In NEUTRINO, the triple therapy of SOF+PEG2a+RBV for 12 weeks led to larger reductions in these measures which mostly persisted to 4 weeks after the end of therapy but had returned to baseline levels by 4 weeks post-therapy. The unpublished abstract[31] reporting HRQoL in VALENCE indicates narratively that the changes in HRQoL were broadly consistent with those seen in the other studies, i.e. HRQoL during SOF+RBV therapy showed a moderate decline relative to baseline but the effect was transient, with HRQoL returning to baseline levels by 12 weeks after the end of treatment. The duration of SOF+RBV therapy (12 or 24 weeks) did not appear to influence HRQoL.

The key conclusions concerning HRQoL are that effects of sofosbuvir-based regimens on HRQoL are transient and do not persist after therapy has ended; HRQoL and productivity are more negatively affected by the inclusion of PEG than by interferon-free regimens; and achievement of SVR12 was associated with improvements in the patient-reported outcome measures.

Subgroup analyses: results for subgroups specified in the NICE scope

Two subgroups are specified in the NICE scope: chronic hepatitis C patients co-infected with HIV, and chronic hepatitis C patients grouped according to their responses to prior therapy.

SVR rates among HIV co-infected patients

One ongoing study (PHOTON-1), on treatment naive and experienced patients with HCV genotypes 1-3, specifically investigated the efficacy of SOF+RBV for 12 or 24 weeks in patients who were co-infected with HIV (but excluded infection with any other hepatitis viruses). The study reported SVR12 in four cohorts according to HCV genotype, treatment history and duration of therapy (Table 11). Sample sizes ranged from 26 to 114 patients in each cohort but, as noted above (section 3.1.4), some patients are missing from the 24 week cohort without explanation and so results should be interpreted with caution. SVR12 rates ranged from 67% to 93% (95% CIs not reported) in the HIV co-infected population. However, PHOTON-1 did not include any mono-infected patients for comparison. Adverse event profiles from PHOTON-1[34] (not reported in the MS) suggest, provisionally, that the safety profile of SOF+RBV for 12 or 24 weeks would be similar in HIV/HCV co-infected and HCV mono-infected patients (see 'Adverse events' below), as the most frequent events were fatigue (35-36% of patients), insomnia (13-21%), nausea (16-18%) and headache (13-14%), and 3-4% of patients required treatment discontinuation due to adverse events.

Table 11 Virologic responses: HIV-co-infected treatment naïve patients with HCV genotypes 1-3

Trial and HCV genotype (GT)	HCV genotype; treatment history	Intervention	Sample size	SVR12, n/N (%)
PHOTON-1 (from MS & Sulkowski et al[34]) GT 1/2/3	1; treatment naive	SOF+RBV 24 weeks	N=114	87/114 (76)
	2; treatment naive	SOF+RBV 12 weeks	N=26	23/26 (88)
	3; treatment naive	SOF+RBV 12 weeks	N=42	28/42 (67)
	2/3; treatment	SOF+RBV 24	N=28	26/28 (93)

	experienced	weeks		

GT: genotype

In summary, only one study has reported SVR12 rates in HIV/HCV co-infected patients and no direct comparison with HCV mono-infected patients is available. The SVR12 data from HIV/HCV co-infected patients should be interpreted with caution as the sample sizes were relatively small, some patients were missing without explanation, and the trial is ongoing, with results being considered interim.

SVR rates according to patients' responses to prior treatment

Three of the 13 included studies (FUSION, POSITRON, VALENCE) presented information on SVR12 rates for different subgroups according to prior treatment response and/or suitability for IFN therapy. These studies were all on patients with HCV genotype 2 and/or 3.

The FUSION trial (treatment experienced patients) reported SVR12 rates for patients according to whether they had not responded to prior interferon (IFN)-based therapy or had relapsed or experienced viral breakthrough. These data are shown in Figure 15 in the MS (p. 109) but precise data values are not given in the MS – the ERG obtained these from the supplementary appendix to the primary publication (p. 33).[32] SVR rates were slightly lower in the non-responder group than the relapse/breakthrough group, for both 12 and 16 week regimens of SOF+RBV, however the differences between response groups were not statistically significant (Table 12).

The POSITRON trial classified a mixed population of treatment naive and experienced patients according to their interferon eligibility based on interferon contraindication, unacceptable side effects, or the patient's decision. This is mentioned narratively in the MS (p. 117) and shown in MS Fig. 17 but quantitative data are given only in the supplementary appendix to the publication[32] which presents SVR12 for the subgroups IFN ineligible, IFN intolerant and IFN unwilling. The SVR rates were similar across these three subgroups, ranging from 76.5% to 78.4% (Table 13). The MS concludes (p. 117) that the specific reason for IFN ineligibility (ineligible, intolerant or unwilling) is not a predictor of SVR12.

Also for a mixed population of treatment naive and experienced patients, the MS (p. 120) reports subgroup analyses from the VALENCE trial, presenting SVR12 rates according to whether patients receiving 12 or 24 weeks of SOF+RBV were classified as interferon-intolerant, non-responders to previous interferon-based therapy, or had experienced relapse or

breakthrough on previous therapy.

[redacted] (Table 14).

Table 12 SVR by prior treatment response subgroups in FUSION (supplementary appendix[32])

SVR12 n/N (%; 95% CI)	SOF+RBV 12 weeks + placebo 4 weeks [a]	SOF+RBV 16 weeks	Proportional difference (95% CI)
Non-response to prior therapy	11/25 (44; 24.4 to 65.1)	16/25 (64; 42.5 to 82.0)	-20.0 (-46.6 to 8.9)
Relapse/breakthrough	39/75 (52; 40.2 to 63.7)	53/70 (75.7; 64.0 to 85.2)	-23.7 (-38.8 to -7.8)

a. FUSION univariate ANOVA, SOF + RBV 12 weeks + 4 weeks placebo:
Non-response to prior therapy versus relapse/breakthrough: OR=0.725 (95% CI 0.292 to 1.803); p=0.49

Table 13 SVR by prior treatment response subgroups in POSITRON (supplementary appendix[32])

SVR12 n/N (%; 95% CI)	SOF+RBV 12 weeks N=207	Placebo 12 weeks N=71	Proportional difference (95% CI)
IFN ineligible	69/88 (78.4; 68.4 to 86.5%)	0/33 (0; 0.0 to 10.6%)	78.4% (67.3 to 86.7%)
IFN intolerant	13/17 (76.5; 50.1 to 93.2%)	0/8 (0; 0.0 to 36.9%)	76.5% (34.9 to 93.2%)
IFN unwilling	79/102 (77.5; 68.1 to 85.1%)	0/30 (0; 0.0 to 11.6%)	77.5% (65.3 to 85.3%)

Table 14 SVR by prior treatment response subgroups in VALENCE (MS p. 120)

SVR12 n/N (%)	GT2 SOF+RBV 12wk N=73	GT3 SOF+RBV 12wk N=11	GT3 SOF+RBV 24wk N=250
[redacted]			

In summary, due to the limited available evidence and small sample sizes involved it is not possible to draw robust conclusions about whether SVR12 rates differ between interferon responders/non-responders or between different classifications of interferon ineligibility.

Subgroup analyses: results for additional subgroups

The MS provides SVR data for two subgroups which are not specified in the NICE scope but which the ERG considers are relevant to the technology appraisal. These are SVR12 according to whether or not patients have cirrhosis, and SVR outcomes for a subgroup of patients receiving SOF+RBV whilst awaiting liver transplant.

SVR rates according to presence or absence of cirrhosis

Patient subgroups with or without cirrhosis are considered relevant since the manufacturer's economic evaluation makes a distinction between cirrhotic and non-cirrhotic patients. These subgroups are not explicitly collated in the MS but are reported in several places within the results of the primary studies (MS p. 96, 102, 110, 117, 120, 125), and in the MTC appendix (Appendix 10.4, Tables 6, 8, 10, 12, 14, 16, 18-21). When considering SVR12 according to cirrhosis status it should be borne in mind that the ATOMIC, ELECTRON and PROTON studies contained only non-cirrhotic patients whilst the remaining studies included varying proportions of non-cirrhotic and cirrhotic patients (section 3.1.3).

Five RCTs (FISSION, FUSION, POSITRON, QUANTUM, SPARE) and four non-RCT studies (VALENCE, NEUTRINO, LONESTAR-2, PHOTON-1) reported SVR12 rates by presence or absence of cirrhosis. Results for QUANTUM and SPARE (both HCV genotype 1) were combined (as reported in the sofosbuvir SmPC[7]). The MS Appendix (p.28-30) cautions that the results from QUANTUM, SPARE and LONESTAR-2 should be interpreted with caution as participant numbers are small and SVR rates may be impacted by the selection of patients, whilst results of PHOTON-1 are specified as being preliminary (Appendix 10.4, Table 20). Excluding subgroups with very small sample sizes (n≤5), rates of SVR12 in both non-cirrhotic and cirrhotic patients ranged from 0% to 100%, depending upon the trial arm, HCV genotype and patient's treatment history. Overall, these studies found that SVR12 rates were either higher in patients without cirrhosis than in those with cirrhosis, or there were only slight differences in SVR12 rates between groups with and without cirrhosis.

The largest difference in SVR12 rates between cirrhotic and non-cirrhotic patients was in the POSITRON trial (MS p. 117) SOF+RBV therapy arm where non-cirrhotic and cirrhotic patients with HCV genotype 3 had SVR12 rates of 68% (57/84) and 21% (3/14) respectively (difference 47%). Relatively large differences also occurred in the FISSION trial (MS p. 104) PEG2a+RBV

(standard of care) arm where non-cirrhotic and cirrhotic patients with HCV genotype 3 had SVR12 rates of 71.2% (99/139) and 29.7% (11/37) respectively (difference 41.5%); and the FUSION trial (MS p. 110) SOF+RBV 12-week therapy arm where non-cirrhotic and cirrhotic patients with HCV genotype 2 had SVR12 rates of 96% (25/26) and 60% (6/10) respectively (difference 36%).

[redacted] When interpreting these results it should be borne in mind that, as indicated above, that some HCV genotype and cirrhosis/non-cirrhosis classes have small sample sizes and also that there were differences among the studies as to whether patients were treatment naive, experienced, or a mixture of the two.

In summary, subgroup analyses suggest that SVR12 rates tended to be lower on average in patients with cirrhosis, and the largest differences in SVR12 rates between cirrhotic and non-cirrhotic patients were among those with HCV genotype 3. However, the findings are heterogeneous, with some studies finding no differences in SVR12 rates; this might reflect uncertainty in actual SVR12 rates as a result of small sample sizes of some of the subgroups analysed.

Patients awaiting liver transplant

The MS (p. 143-144) presents SVR results for the study that included patients with chronic hepatitis C awaiting liver transplant (P7977-2025) (MS p. 143-144). The outcome is referred to as post-transplant virologic response (ptVR12), defined as an SVR achieved 12 weeks after transplant for patients who had a virologic response (HCV RNA) at their last pre-transplant HCV RNA measurement. The trial excluded participants with signs of decompensated cirrhosis and most participants (75%) had received prior therapy for HCV. Participants received SOF+RBV for up to 48 weeks or until liver transplant. The results are referred to as an interim analysis (MS p. 143) and indicate that the pre-transplant SOF+RBV regimen resulted in ptVR12 in 64% of 41 participants who had achieved a virologic response pre-transplant. This compares favourably with the historical risk of HCV reinfection in the absence of HCV prophylaxis (described in the MS as ‘near universal’) but as this was a single-cohort study it is not possible to compare the efficacy of SOF+RBV in this population against an alternative prophylactic regimen (i.e. PEG+RBV).

In summary, sofosbuvir appears to have favourable efficacy for HCV prophylaxis in patients awaiting liver transplant. However, the only available data are from a single cohort in an ongoing study. No comparisons are available in this population for sofosbuvir-based and non-sofosbuvir therapies.

Adverse events

The MS provides data on adverse events for five of the phase 3 studies (NEUTRINO, FISSION, FUSION, POSITRON, VALENCE). Further detailed accounts of adverse events are given in the literature for five of the eight included phase 2 studies (SPARE, PROTON, ATOMIC, ELECTRON, P7977-2025) and (as noted above) the phase 3 PHOTON-1 trial, but these are not considered in the MS. The ERG has checked whether the adverse events reported in the phase 2 trial publications provide any additional information relevant to the MS. Both the phase 3 and phase 2 studies reported adverse events consistent with the use of RBV (±PEG2a). With the exception of treatment discontinuations being notably more frequent in a specific arm of one phase 2 RCT (see below), adverse events did not differ substantially between the phase 2 or phase 3 studies.

Common adverse events

The phase 2 studies generally agree with the phase 3 studies that the most common adverse events among chronic hepatitis C patients receiving SOF+RBV therapy (±PEG2a) are fatigue, headache, anaemia, nausea, insomnia, irritability, rash, pruritis, myalgia, decreased appetite, influenza-like illness, chills, pyrexia, and neutropenia. Among these events, fatigue and headache were usually the most frequent, affecting >40% of the patients in some studies.

In the phase 3 RCT head-to-head comparison of SOF+RBV (12 weeks) against PEG2a+RBV (24 weeks) (FISSION trial; HCV genotype 2/3 treatment naive patients), the common adverse events that occurred in ≥10% of patients in at least one group were consistently more frequent in the PEG2a RBV group. Where SOF+RBV was compared against an inactive placebo (phase 3 POSITRON trial; HCV genotype 2/3 treatment experienced and treatment naive patients), common adverse events occurred either more frequently in the SOF+RBV group than the placebo group or at similar frequencies in both groups.

Serious adverse events

The proportion of patients on sofosbuvir-based therapy who experienced serious adverse events ranged from 0% in the phase 2 ELECTRON trial (SOF+RBV or SOF+PEG2a+RBV for

12 weeks) [redacted] (SOF+RBV for 12 weeks) up to 18% in the phase 2 P7977-2025 trial on pre-liver transplant patients receiving 12-48 weeks of SOF+RBV, although the trial publication states that none of the serious AEs were sofosbuvir-related.[35] In the remaining studies the frequency of serious adverse events ranged from 3% to 7%. Where adverse events were classified as grade 3+4 events in the non-head-to-head studies these ranged in frequency from [redacted] in the phase 3 VALENCE trial (SOF+RBV for 12 weeks) to 15% in the phase 3 NEUTRINO trial (SOF+PEG2a+RBV for 12 weeks).

In the phase 3 RCT head-to-head comparison of SOF+RBV (12 weeks) against PEG2a+RBV (24 weeks) (FISSION trial; HCV genotype 2/3 treatment naive patients), grade 3+4 adverse events were more frequent in the PEG2a+RBV group (18.5% and 7% respectively).

Treatment discontinuations

The proportion of patients on sofosbuvir-based therapy experiencing treatment discontinuation due to adverse events varied across the studies from 0% in the FUSION trial (SOF+RBV 12 or 16 weeks), SPARE trial (SOF+RBV 24 weeks) and ELECTRON trial (SOF+RBV or SOF+PEG+RBV for 12 weeks) to 18% in the ATOMIC trial (SOF+PEG2a+RBV for 24 weeks). For the remaining studies the proportion discontinuing treatment ranged from 1% to 6%. The relatively high rate of 18% treatment discontinuation in the ATOMIC trial was in treatment naive patients of HCV genotype 1 and may reflect an effect of the 24-week treatment duration of SOF+PEG2a+RBV, since patients in the 12-week SOF+PEG2a+RBV arm experienced only a 6% rate of treatment discontinuation.

In the RCT head-to-head comparison of SOF+RBV (12 weeks) against PEG2a+RBV (24 weeks) (FISSION trial; HCV genotype 2/3 treatment naive patients), treatment discontinuations due to adverse events were more frequent in the PEG2a+RBV group (11% versus 1%).

In summary, the adverse events associated with sofosbuvir-based regimens were as would be expected for regimens containing ribavirin with or without peginterferon. The most frequent adverse events were headache and fatigue. In the head-to-head comparison of SOF+RBV against PEG2a+RBV the sofosbuvir-based regimen resulted in fewer adverse events and fewer treatment discontinuations due to adverse events, suggesting an improved safety profile compared to standard of care.

3.4 Summary

Included studies

The manufacturer's systematic review of clinical effectiveness is of a reasonable quality and contained 13 studies examining the efficacy of sofosbuvir in treating chronic hepatitis C that had been used to inform the licensing recommendations. Seven studies compared different treatment regimens of sofosbuvir combined with RBV or PEG2a/RBV and/or different treatment durations, and four studies had single arms. Most of these studies do not directly address NICE's final scope, but do provide data on SVR rates for patients treated with sofosbuvir, across different genotypes and treatment combinations, and helped to determine treatment durations for the marketing authorisation.

Only one study directly meets NICE's final scope: FISSION, which compared SOF+RBV for 12 weeks against current standard of care (PEG2a+RBV for 24 weeks in treatment naïve genotype 2 and 3 patients). Additionally, one study (POSITRON), on a mixed population of HCV genotype 2/3 treatment experienced and treatment naive patients, that compared sofosbuvir with a true (i.e. inactive) placebo would meet the scope if the placebo arm is assumed to approximate best supportive care (i.e. no treatment).

The head-to-head trial showed that SOF+RBV for 12 weeks had similar efficacy (was statistically non-inferior) to PEG2a+RBV for 24 weeks (SVR12 67% in both groups); in subgroup analyses SOF+RBV for 12 weeks was more effective than PEG2a+RBV for 24 weeks in treating genotype 2 but not genotype 3 patients. (Note SOF+RBV is licensed for treatment in genotype 3 patients over 24 rather than 12 weeks.)

SVR12 frequencies in sofosbuvir regimens of the included studies ranged from [redacted] to 100%, depending upon the sofosbuvir regimen, duration of therapy, and treatment history of the patients.

Subgroup analyses

One study investigated sofosbuvir in chronic hepatitis C patients co-infected with HIV, finding that SVR12 ranged from 67% in HCV genotype 3 treatment naive patients receiving 12 weeks of SOF+RBV to 93% in combined HCV genotype 2/3 treatment experienced patients receiving 24 weeks of SOF+RBV. Limitations are that the trial is ongoing, did not include HCV mono-

infected patients for direct comparison, and in one of the study cohorts some patients are missing without explanation.

Three studies, all on populations of patients with HCV genotypes 2 and/or 3, provided SVR12 rates for subgroups according to patients' previous responses to treatment. Due to limitations of the evidence it is not possible to draw any robust conclusions about whether SVR12 differs consistently between patients who had not responded to prior IFN-based therapy and those who had responded but relapsed or experienced viral breakthrough; or between patients who were classed as IFN ineligible, IFN intolerant or IFN unwilling.

Nine studies reported SVR by cirrhosis status subgroups. Excluding subgroups with very small sample sizes (n≤5), SVR rates ranged overall from 0% to 100% in both non-cirrhotic and cirrhotic patients, depending upon study, HCV genotype and patient's treatment history. SVR12 rates were on average higher in patients without cirrhosis than in those with cirrhosis, with the largest differences found in patients with HCV genotype 3. However, in some studies there was no clear difference in SVR12 between the subgroups; this may reflect uncertainty in actual SVR12 estimates in cases where numbers of patients in the subgroups were very small.

The manufacturer's interpretation of the evidence is on the whole justified and unbiased However, the ERG considers that most of the evidence does not directly address the decision problem, due to the lack of head-to-head studies against current standard of care comparators, and has identified the following uncertainties:

- No studies have examined the efficacy of sofosbuvir within its licenced indication in treating HCV genotype 1 treatment experienced patients, a patient group who have a high unmet treatment need.
- Data supporting the treatment regimens licensed for use in genotype 3 patients come from two small phase 2 studies and only the VALENCE Phase 3 trial. VALENCE results need to be interpreted with caution because randomisation was broken, with HCV genotype 3 patients switched from 12 to 24 weeks of SOF+RBV part the way through the trial and 11 genotype 3 patients were not moved over to 24 weeks of therapy. It is uncertain what the SVR12 rate would have been if these patients had been included in the 24 week therapy arm.

- HRQoL results have uncertain relevance in the FISSION trial because they are presented for an unexplained subgroup of the trial participants, and in the VALENCE trial because only unpublished summary results are available.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of treatments for HCV.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of SOF+RBV +/- PEG2a is reported in different genotype subgroups compared to: PEG2a and RBV; telaprevir, PEG2a and RBV; and boceprevir, PEG2b and RBV as appropriate to their respective licensed indications.

Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify all published studies that assessed the cost-effectiveness of treatments currently used for HCV (see section 3.1.1 of this report for the ERG critique of the search strategy). In addition a manual search of reference lists of systematic reviews was conducted.

The inclusion and exclusion criteria for the systematic review are listed in MS Table 37 (MS p. 163). The inclusion criteria state that economic evaluations, health technology assessments and systematic reviews of HCV screening programmes, HCV treatments (PEG-IFN, RBV, sofosbuvir, telaprevir, or boceprevir) or watchful waiting would be included. The population of interest was adults (aged > 18 years) infected with HCV genotypes 1-6 who could be treatment naive or treatment experienced. The review also included patients co-infected with HIV. Eligible outcomes were costs, resource use, quality-adjusted life years (QALYs), life years gained (LYG) and productivity losses. The exclusion criteria are listed in Table 37 of the MS (p163). Key criteria of note are that studies with small samples (<10), those with populations with recurrent HCV, HCV/HBV co-infected, depression or homeless populations and intravenous drug users were excluded. Studies published in English, French, German, Spanish and Italian were included.

1475 unique references were identified from searches and their abstracts were reviewed. In response to a clarification question the manufacturer confirmed that 326 papers were selected for full text review (there was an error in the MS figure 19, MS p. 164). Of these 112 were included. No relevant studies of sofosbuvir were identified. The quality of cost effectiveness studies was assessed using a series of questions which were based on the format developed by Drummond and Jefferson[39] (MS Appendix 10.11). Overall, there is limited discussion of how the studies included inform the choice of economic model used and the MS does not make any general conclusions about the findings of the systematic review.

CEA Methods

The cost effectiveness analysis (CEA) uses a Markov state-transition model to estimate the cost-effectiveness of sofosbuvir for a number of different patient groups (see section 4.2.1 below for details). The model was adapted from the model used in previous technology appraisals (and taken from Bennett and colleagues 1997[40]). The model adopts a lifetime horizon (until patients reach 100 years), with an annual cycle length (except in the first two years where a 3 month cycle was used). Patients enter the model from either a non-cirrhotic health state or a compensated cirrhosis (CC) health state. There are four other liver related health states (decompensated cirrhosis [DC], liver transplant, post liver transplant and hepatocellular carcinoma [HCC]) and a health state for death. Treatment effect data were based on the SVRs taken from the sofosbuvir clinical trials and where data for SVRs of comparators were not available in these trials they were taken from other studies identified by the manufacturer. The main determinants of quality of life in the model were taken from utilities from the UK mild chronic hepatitis C trial.[41]

NHS reference costs were used, consistent with previous NICE assessments. Costs reflect the NHS and Personal Social Services (PSS) perspective and have four components: treatment costs; adverse event costs; health state costs; and monitoring costs.

The results from the economic evaluation are presented for the base case assumptions [see MS Table 81 (MS p. 246) and MS Tables 82-92 (MS p. 248-251)]. The key assumptions (see MS p. 170 and 208) are that patients enter the model in either a non-cirrhotic or compensated cirrhosis state; non-cirrhotic and cirrhotic patients with an SVR have zero risk of progression to more severe health states; those without SVR have an annual probability of progressing as if they had not received antiviral treatment; different health states relating to decompensated cirrhosis are

aggregated together; patients do not progress while on treatment or during the 12 or 24 weeks after treatment; and non-cirrhotic patients with an SVR are only followed up until the end of year two. The MS presents base case results for HCV genotype subgroups, for treatment history (treatment naive or experienced) and eligibility for PEG2a treatment. In the NICE scope two subgroups were noted, co-infection with HIV and response to previous treatment (non-response, partial response, relapsed). The MS states (p. 168) that it is anticipated that the HIV co-infected population respond to sofosbuvir-based regimens in a similar manner to the mono-infected population with respect to safety and efficacy (see section 4.2.2). However, the MS does present some subgroup analyses for HCV/HIV co-infected patients based on evidence from one trial in an Appendix (10.14.8), p498-500. The MS reported that the model underwent internal and external validation.

Assessment of uncertainty

Deterministic sensitivity analyses (DSA) were performed to test structural assumptions. One-way sensitivity analyses were used for most inputs. Those tested in multi-way sensitivity analyses are described on MS p. 234-237. Structural uncertainty was assessed by including the possibility of recurrence or re-infection for non-cirrhotic and cirrhotic patients that reach SVR. Probabilistic sensitivity analysis (PSA) was also undertaken; Table 69 (MS p. 246-8) reports the parameters and distributions applied.

CEA Results

Results are presented as the incremental cost per QALY for sofosbuvir against each comparator within each treatment subgroup of HCV genotype, treatment history and PEG eligibility (MS Table 81). In addition, the ICERs are presented for each treatment against the least expensive comparator in MS Tables 82-92 (pp248-251).

Results of the manufacturer's model show that sofosbuvir is a cost-effective treatment option in the majority of subgroups presented. Base case ICERs are shown in Table 15. In most cases the ICERs are below £30,000 per QALY gained. The exceptions are HCV genotype 1 treatment naive patients who are unsuitable for PEG (ICER £49,249) and treatment naive patients with HCV genotype 2 (ICER £46,324). No analysis of HCV genotype 1 treatment experienced patients was undertaken in the MS. The manufacturer provided an analysis in response to a request for clarification, and this is discussed below in section 4.3.

Across all results the ICERs are sensitive to the discount rates for both costs and outcomes and the utility increment after an SVR is achieved.

MS Tables 203-207 (MS appendix p. 501-2) report the ICERs for sofosbuvir against each comparator for the HIV co-infected population for HCV genotypes 1, 2 and 3. These are reproduced here in Table 16 where it can be seen that sofosbuvir is not cost-effective in any of the comparisons respectively.

Table 15 MS Base case cost effectiveness results: Fully incremental results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYGs[a]	Incremental QALYs[a]	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT1 TN IFN eligible								
PEG2a+RBV (48 wks)	£24,994	19.3	13.8	NA	NA	NA	NA	NA
Telaprevir+PEG2a+RBV	£38,835	19.9	14.6	£13,841	0.6	0.8	£16,587	Extended dominance
Boceprevir+PEG2b+RBV	£39,221	19.8	14.4	£14,227	0.4	0.6	£23,360	Dominated
SOF+PEG2a+RBV (12 wks)	£44,123	20.2	15.1	£19,129	0.9	1.3	£14,930	£14,930
GT1 TN unsuitable for IFN								
No treatment	£20,225	18.7	13.0	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£84,129	19.5	14.3	£63,903	0.8	1.3	£49,249	£49,249
GT2 TN IFN eligible								
PEG2a+RBV (24 wks)	£14,492	21.1	15.6	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£42,271	21.6	16.2	£27,779	0.5	0.6	£46,324	£46,324
GT2 TN unsuitable for IFN								
No treatment	£21,426	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,477	20.4	15.3	£20,051	1.8	2.5	£8,154	£8,154
GT2 TE IFN eligible								
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
PEG2a+RBV (48 wks)	£24,022	19.3	13.7	£3,251	0.7	0.9	£3,778	£3,778
SOF+RBV (12 wks)	£42,269	20.2	15.1	£21,498	1.6	2.3	£9,274	£12,519
GT2 TE unsuitable for IFN								
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,468	20.3	15.2	£20,697	1.7	2.4	£8,591	£8,591
GT3 TN IFN eligible								
PEG2a+RBV (24 wks)	£19,704	20.3	14.7	NA	NA	NA	NA	NA
SOF+PEG2a+RBV (12 wks)	£44,674	21.5	15.9	£24,970	1.2	1.2	£20,613	£20,613
GT3 TN unsuitable for IFN								
No treatment	£23,406	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£78,543	20.3	15.0	£55,137	2.1	2.6	£21,478	£21,478
GT3 TE IFN eligible								
No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA

PEG2a+RBV (48 wks)	£25,531	19.1	13.4	£2,791	0.9	0.9	£3,037	£3,037
SOF+PEG2a+RBV (12 wks)	£42,374	20.1	14.7	£19,634	1.9	2.3	£8,557	£12,246
GT3 TE unsuitable for IFN								
No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£81,568	19.8	14.5	£58,828	1.5	2.1	£28,569	£28,569
GT4/5/6 TN								
PEG2a+RBV (48 wks)	£22,631	19.5	13.9	NA	NA	NA	NA	NA
SOF+PEG2a+RBV (12 wks)	£46,573	19.8	14.8	£23,942	0.3	0.9	£26,797	£26,797

[a]for SOF regimens relative to the comparator within each treatment indication

Dominated: treatment is more costly and less effective than alternative treatment. Extendedly dominated: treatment produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks

Table 16 MS Base case results for the HIV co-infected population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT1 TN HCV/HIV co-infected								
No treatment	£22,473	18.4	12.6	NA	NA	NA	NA	NA
PEG2a+RBV (48 wks)	£27,141	19.1	13.4	£4,669	0.7	0.8	£5,846	£5,846
SOF+RBV (24 wks)	£78,883	19.8	14.6	£56,411	1.4	2.0	£28,504	£43,836
GT2 TN HCV/HIV co-infected								
PEG2a+RBV (48 wks)	£20,303	19.8	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,380	20.2	13.2	£21,078	0.4	0.4	£55,867	£55,867
GT2 TE HCV/HIV co-infected								
PEG2a+RBV (48 wks)	£19,485	19.8	12.9	NA	NA	NA	NA	NA
No treatment	£32,031	17.0	9.1	£12,546	-2.7	-3.7	Dominated	Dominated
SOF+RBV (24 wks)	£76,280	20.3	13.3	£56,795	0.5	0.4	£128,248	£128,248
GT3 TN HCV/HIV co-infected								
PEG2a+RBV (48 wks)	£21,571	19.7	12.4	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£49,904	19.2	11.8	£28,333	-0.4	-0.6	Dominated	Dominated
GT3 TE HCV/HIV co-infected								
PEG2a+RBV (48 wks)	£20,686	19.7	12.5	NA	NA	NA	NA	NA
No treatment	£33,176	16.8	8.9	£12,491	-2.8	-3.6	Dominated	Dominated
SOF+RBV (24 wks)	£78,399	20.2	13.1	£57,713	0.5	0.6	£90,822	£90,822

GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks

The MS undertook PSA on each HCV genotype and treatment history subgroup and presents the results of 1000 simulations for each comparator treatment in a series of figures (MS p. 282-296). The MS summarises the results of the PSA stating that there is a range of probabilities of SOF being cost-effective at a threshold WTP of £20,000 and £30,000 per QALY gained. These have been tabulated by the ERG for ease of reference (Table 17).

Table 17 Results of manufacturer PSAs

Intervention	Comparator	Probability cost-effective at £20,000/QALY	Probability cost-effective at £30,000/QALY
GT1 TN IFN eligible			
SOF+PEG2a+RBV	PEG2a+RBV	63%	90%
	Telaprevir+ PEG2a +RBV	68%	85%
	Boceprevir+ PEG2b +RBV	85%	95%
GT1 TN unsuitable for IFN			
SOF+RBV	No treatment	<5%	10%
GT2 TN IFN eligible			
SOF+RBV	PEG2a+RBV	<5%	10%
GT2 TN unsuitable for IFN			
SOF+RBV	No treatment	98%	100%
GT2 TE IFN eligible			
SOF+RBV	No treatment	95%	100%
	PEG2a+RBV	78%	95%
GT2 TE unsuitable for IFN			
SOF+RBV	No treatment	97%	100%
GT3 TN IFN eligible			
SOF+PEG2a+RBV	PEG2a+RBV	37%	80%
GT3 TN unsuitable for IFN			
SOF+RBV	No treatment	30%	80%
GT3 TE IFN eligible			
SOF+ PEG2a+RBV	No treatment	96%	100%
	PEG2a+RBV	75%	98%
GT3 TE unsuitable for IFN			

SOF+RBV	No treatment	12%	48%
GT4/5/6 TN			
SOF+ PEG2a+RBV	PEG2a+RBV	24%	50%

GT: genotype; IFN: interferon; TE: treatment experienced; TN: treatment naive

The MS concludes that sofosbuvir-based regimens offer a favourable cost-effectiveness profile compared with current standards of care (MS p. 39).

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

Manufacturer's review of published economic evaluations

The MS presents a systematic review of published economic evaluations. The systematic review appears to have used a comprehensive search for studies and the methods appear to be reasonable, although only a selection of included studies was quality assessed. In response to a clarification question the manufacturer confirmed that only 61 studies were relevant as other studies included budget impact methods, cost and cost-minimisation studies. No interpretation or conclusions of this quality assessment were provided in the MS (MS p.167 refers only to the appendix, but the appendix reports only the tables); therefore, of the reviewed studies it is not clear what the overall impression of study quality was or what the key issues may have been. However, as stated above, no studies of sofosbuvir were identified.

Critical appraisal of manufacturer's submitted economic evaluation

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 18 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[39]). The critical appraisal checklist indicates that overall the manufacturer follows recommended methodological guidelines.

Table 18 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	In line with the NICE scope, although one genotype subgroup comparison is omitted
Is there a clear description of alternatives?	Yes	All comparators in line with the scope and previous guidance in the disease area.
Has the correct patient group / population of interest been clearly stated?	Yes	For base case population: • adults with chronic hepatitis C by genotype group, treatment history and eligibility for treatment with

		interferon • as per the marketing authorisation *(Discussed in section 4.2.2)*
Is the correct comparator used?	Yes	Scoped comparators (PEG2a or 2b with RBV; telaprevir; boceprevir; best supportive care) were all included. *(Discussed in section 4.2.3)*
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	NHS and Personal Social Services (PSS)
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	A lifetime horizon (until patients reach 100 years) is used. *(Discussed in section 4.2.1)*
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	3.5% for costs and health benefits as per NICE recommendations. Tested in sensitivity analysis at 0% and 6%.
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 19. The ERG considers that the submitted evaluation conforms to the NICE reference case.

Table 19 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	Although one genotype subgroup is omitted the submission meets the NICE scope.
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	

Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	
Source of preference data: Representative sample of the public	Yes	
Discount rate: 3.5% per annum for costs and health effects	Yes	

Overall the methods in the MS appear to be reasonable and the methods and data inputs conform to NICE's methodological guidance.

4.2.1 Modelling approach / Model Structure

A Markov state-transition model was adapted from the model by Bennett and colleagues[40] and is based on the previous economic models developed by SHTAC in the UK for NICE.[42;43] A schematic of the model is given in Figure 1. Dotted lines indicate transitions which are only examined in sensitivity analyses and which are not included in the base case.

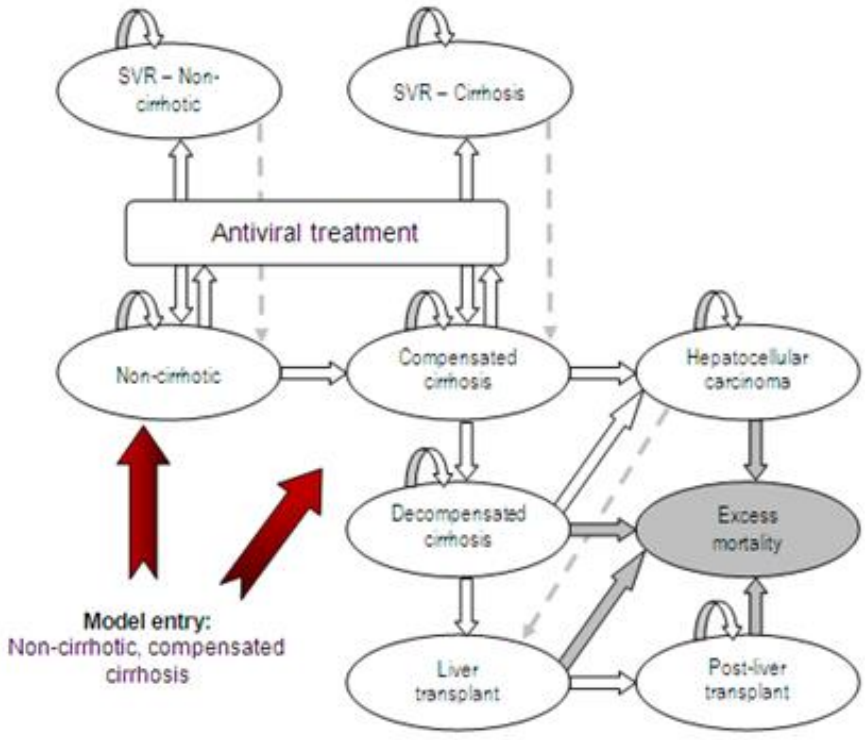

Figure 1. Schematic of manufacturer's model for chronic hepatitis C (reproduced from MS Figure 20, MS p. 169)

Patients start the model in either the non-cirrhotic or compensated cirrhosis health states. Non-cirrhotic and cirrhotic patients move respectively to the SVR-Non-cirrhotic and SVR-Cirrhotic health states after completing treatment if they have undetectable HCV RNA at 12 or 24 weeks after the end of treatment. Patients with an SVR are assumed to no longer face a probability of progressing through the disease. However, recurrence and re-infection with HCV are considered in sensitivity analysis (MS p. 170). Patients without an SVR may progress from no cirrhosis to compensated cirrhosis, and from compensated cirrhosis to either hepatocellular carcinoma (HCC) or decompensated cirrhosis. Patients in the decompensated cirrhosis state may move to the HCC state; die from liver disease; or undergo a liver transplant. Patients in the HCC state may also undergo liver transplant although this is only examined in a sensitivity analysis. Following liver transplant, patients face a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase, HCC and decompensated cirrhosis health states patients remain at a higher risk of death compared to the general population. Age-specific general population mortality rates are applied to each health state in the model although for clarity this is not represented in Figure 1.

The MS notes that the sofosbuvir economic model amends the model produced by SHTAC by combining both mild and moderate HCV patients into the non-cirrhotic health state. This was done in order to reflect the data available from the key trials, where no distinction was made between mild and moderate patients (MS p. 170). A further modification, not well documented in the MS, is that transition from the SVR-Cirrhotic health state to HCC is not included in either the base case or sensitivity analysis. Clinical advice to the ERG is that this transition should have been included in order to reflect the biological process of the disease (see section 4.3).

Other structural assumptions made by the model are that the potential occurrence of decompensated cirrhosis among patients with HCC is ignored (MS p. 170); non-cirrhotic HCV patients with SVR have zero risk of developing HCC (MS p. 207); patients do not die during the treatment period (MS p. 208); and that patients with compensated cirrhosis that achieve SVR are followed up over a lifetime, but that non-cirrhotic patients with SVR are only followed until the end of year two. Clinical advice to the ERG agrees that after successful treatment non-cirrhotic patients are discharged, while cirrhotic patients continue to be monitored for progression.

The ERG notes that the treatment period extends to 36 weeks for sofosbuvir for the purpose of mortality calculation regardless of whether a 12 week or 24 treatment duration is being considered. The treatment period extends to 48 weeks for all comparators (including no treatment) for the purpose of mortality calculation. However, whilst the model does not reflect treatment periods accurately in this respect, the ERG considers that this is conservative because mortality after treatment is applied sooner for sofosbuvir than for comparators.

The MS states that internal validation of the model was conducted through model checking by two modellers and a senior statistician. External validation was undertaken with one clinical expert from England (MS p. 298).

The model has a lifetime horizon of either 55 or 60 years depending on the modelled indication (MS Table 41, p. 172 and MS Table 44, p. 182). SVR status at 12/24/48 weeks is extrapolated to age 100 using probabilities obtained from the literature and previous HTAs on HCV.

Cycle length is three months for the first two years and annual thereafter (MS Table 41 p. 173). The MS states that a shorter cycle length is adopted in the first two years as sofosbuvir is administered for either 3 or 6 months (12 or 24 weeks) which results in SVR12 measured at 6 or 9 months and SVR24 at 9 or 12 months (MS Table 41, p. 173). A cycle length of 1 year is consistent with the SHTAC model and previous HTAs.[42] A half-cycle correction was applied and again this is consistent with previous HTAs.

In general the ERG considers that the modelling approach adopted in the submission is reasonable and is consistent with the sources of evidence used in its development. One limitation is that a transition is not included from the SVR-Cirrhotic health state to the HCC health state. This is considered by the ERG in additional work described in section 4.3.

4.2.2 Patient Group

As noted above, the economic evaluation reports all major HCV genotype subgroups. The groups are further divided into treatment history (naive or experienced) and eligibility for treatment with PEG2a, with the exception of genotype 1 where no modelling was undertaken of the treatment experienced group in the original submission (exploratory modelling of this group is described in the manufacturer's clarification letter and is discussed further in section 4.3).

The patient group included in the economic evaluation is adults with HCV and this appears to reflect the NICE scoped population. Few details of the model baseline population are reported in the MS and the baseline characteristics from the sofosbuvir trials do not appear to have informed the characteristics of the starting population in the economic model. The proportion with cirrhosis (and therefore non-cirrhosis, defined as 100% minus the % cirrhotic) was obtained from the HCV UK research database.[44] The MS (p.177) discusses the use of the HCV UK research database which has 5000 anonymised patient records and the MS states this reflects real-life practice in terms of the cirrhotic status of the starting population. The MS reports that this was a conservative approach compared to expert opinion which had suggested that the cirrhotic population was significantly higher, particularly in the HCV genotype 3 population (suggested to be 50%). The ERG clinical advisors agree that the use of the HCV UK database is appropriate. The mean age (either 40 or 45 years) and weight (79kg) were taken from the previous HTAs on chronic hepatitis C and are .[42]

The proportion cirrhotic, the mean age at treatment, and the mean weight for patients within each subgroup (HCV genotype, treatment history, and interferon eligibility) are presented in MS Table 44 (MS p.182). The HCV genotype and treatment history of participants are indicated by the respective subgroups for sofosbuvir treatment. There is no discussion in the MS of the model baseline male to female ratio or the ethnicity of the populations. The patient population appears to reflect those covered in the licensed indication for sofosbuvir (with the exception of HCV genotype 1 treatment experienced patients who were not included in the analysis). As such the ERG believes that the patient population is likely to reflect the target population in current clinical practice.

The MS model includes only HCV mono-infected populations. The MS states that they anticipate that HCV/HIV co-infected populations will respond in a similar manner to sofosbuvir treatment. The MS provides support for this comparing (by observation) the treatment effects from various clinical trials to those seen in the one clinical trial which had co-infected patients (MS p.168). An analysis of the co-infected populations is presented in an appendix of the MS (Appendix 10.14.8). However, the ERG notes that the transition probabilities in the model are different when there is HIV co-infection and, therefore, that this subgroup should not be assumed to be accurately reflected in the base case.

4.2.3 Interventions and comparators

The intervention is sofosbuvir in combination with PEG2a and RBV or with RBV alone. The recommended dose of sofosbuvir is 400mg once a day. The treatment duration is either 12 or 24 weeks according to HCV genotype group and PEG eligibility. In those with HCV genotypes 1 or 3-6, sofosbuvir is combined with PEG2a and RBV for 12 weeks, except where PEG is unsuitable, in which case sofosbuvir is combined with RBV and administered for 24 weeks. In those with HCV genotype 2, sofosbuvir and RBV are administered for 12 weeks.

A range of comparators were used, all of which are relevant to current UK practice and correspond to the NICE scope. The comparators are telaprevir, boceprevir, and PEG2a with RBV. MS p173 states that these were in line with their respective marketing authorisations and the ERG concurs with this. The ERG clinical advisors have confirmed that the comparators are routinely used in UK NHS. For genotype 1 patients telaprevir is used more often than boceprevir, and the use of PEG-IFN and RBV therapy in this genotype group is limited. For genotype 2 or 3 PEG-IFN and RBV are standard therapy. The MS also reports that as evidence has demonstrated similar efficacy between peg-interferon 2a and 2b only the former (2a) is modelled. This appears appropriate (2b is more expensive than 2a) although for completeness it would have been better for a sensitivity analysis to have been undertaken to address this. A sensitivity analysis was carried out by the ERG for some indications and is described in section 4.3.

4.2.4 Clinical Effectiveness

The key clinical event affected by sofosbuvir in the economic model is the proportion achieving SVR. This was obtained for each patient group by genotype from the corresponding sofosbuvir studies where possible, but otherwise relevant figures identified in the MTC systematic literature review were used (MS p. 177). Details of the SVR calculation and data sources are presented in MS Tables 45 to 55 (MS p. 185-205). Other outcomes obtained from the key trials are treatment duration and adverse events. These outcomes are also given in MS Tables 45 to 55 for the various HCV genotypes (MS p. 185-205). Ranges for the parameters used in deterministic sensitivity analyses are given in MS Table 68 (MS p. 235).

SVR enters the model as a baseline probability of response within the relevant treatment period. Different probabilities are used for patients with and without cirrhosis at the start of treatment. SVR estimates are presented for each combination of HCV genotype, treatment experience and

interferon eligibility considered in the base case (11 indications, 15 pairwise comparisons). These are summarised in Table 20.

Table 20. Summary of genotype-specific SVR proportions (%) applied in the economic model (adapted from MS Tables 45-55)

Treatment	Treatment duration (weeks)	SVR (%) for non-cirrhotic	SVR (%) for cirrhotic	SVR-12 or SVR-24	Source
HCV genotype 1, treatment naive, interferon eligible					
SOF+ PEG2a+RBV	12	91.7	80.8	SVR-12	NEUTRINO
PEG2a+RBV	48	43.6	23.6	SVR-24	McHutchison et al 2009[45]
TELAPREVIR+ PEG2a +RBV		75.4	61.9	SVR-24	Telaprevir NICE STA[2]
BOCEPREVIR+ PEG2b +RBV		64.1	55.0	SVR-24	Lawitz et al 2012[46]
HCV genotype 1, treatment naive, unsuitable for interferon					
SOF+RBV	24	67.6	36.4	SVR-12	QUANTUM and SPARE
No treatment		0	0		
HCV genotype 2, treatment naive, interferon eligible					
SOF+RBV	12	96.7	85.7	SVR-12	VALENCE and FISSION
PEG2a+RBV	24	81.5	61.5	SVR-24	FISSION
HCV genotype 2, treatment naive, unsuitable for interferon					
SOF+RBV	12	93.4	94.7	SVR-12	VALENCE and POSITRON
No treatment		0	0		
HCV genotype 2, treatment experienced, interferon eligible					
SOF+RBV	12	91.5	82.4	SVR-12	SVR-12 from VALENCE and FUSION
PEG2a+RBV	48	35.0	35.0	SVR-24	Lagging et al 2013;[47] Shoeb et al 2011[48]
No treatment		0	0		
HCV genotype 2, treatment experienced, unsuitable for interferon					

SOF+RBV	12	92.0	92.0	SVR-12	VALENCE and POSITRON
No treatment		0	0		
HCV genotype 3, treatment naive, interferon eligible					
SOF+PEG2a+RBV	12	97.4	83.3	SVR-12	ELECTRON and PROTON; LONESTAR-2 for non-cirrhotic
SOF+RBV	24	93.5	92.3	SVR-12	VALENCE
PEG2a+RBV	24	71.2	29.7	SVR-24	FISSION
HCV genotype 3, treatment naive, unsuitable for interferon					
SOF+RBV	24	93.5	92.3	SVR-12	VALENCE
No treatment		0	0		
HCV genotype 3, treatment experienced, interferon eligible					
PEG2a+RBV	12	83.3	83.3	SVR-12	LONESTAR-2
SOF+RBV	24	85.0	60.0	SVR-12	VALENCE
PEG2a+RBV	48	35.0	35.0	SVR-24	Lagging et al 2013;[47] Shoeb et al 2011[48]
No treatment		0	0		
HCV genotype 3, treatment experienced, unsuitable for interferon					
SOF+RBV	24	85.0	60.0	SVR-12	VALENCE
No treatment		0	0		
HCV genotypes 4/5/6, treatment naive					
SOF+ PEG2a+RBV	12	100	50.0	SVR-12	NEUTRINO
PEG2a+RBV	48	50.0	38.6	SVR-24	Manns et al 2001[49]

The MS does not provide a clear description of how each study providing these estimates was sourced, or any justification for the choice of studies. The ERG has checked the studies used to establish whether they are the most valid source of evidence, and checked data from each source. Many of the estimates come from single arms of RCTs which were not linked through any statistical methods to one another; non-RCTs; or small subgroup analyses. The ERG therefore suggests caution is applied when interpreting these model outcomes based upon these data.

The ERG note an error in the SVRs reported for the GT2 TE IFN eligible group as reported in the SmPC. The SVR reported for the FUSION RCT appears to be the 16 week SVR. Using the 12 week SVR would lead to the non-cirrhotic SVR being 90.3% (from 91.5%) and the cirrhotic SVR being 72% (from 82.4%). This is further complicated by the MS reporting the non-cirrhotic SVR from the FUSION trial differently than the SmPC (MS Table 26, p110 reports 25/26, SmPC reports 26/29) and it is therefore unclear which is the correct estimate. (The ERG found that these alternative SVRs do not substantively change model outcomes.) The MS reports the use of data from Shoeb and colleagues[48] for PEG2a in GT2 TE IFN eligible and GT3 TE IFN eligible. However the ERG has been unable to identify these data in the Shoeb and colleagues publication and have been unable to source any alternative data.

For sofosbuvir the MS applies data from the relevant clinical effectiveness trials, as reported in section 3. In some cases estimates are combined from more than one trial using a simple average (e.g GT2 TN IFN eligible combines estimates from VALENCE and FISSION) and for some genotype subgroups the estimates were taken from non-RCTs (e.g GT1 TN IFN eligible from NEUTRINO). In the case of the genotype 3, treatment naive IFN eligible group two non-RCT estimates were combined using a simple average. As noted above, in most cases the estimates were from single arms and/or subgroups only.

For the comparator evidence the MS applies data from various clinical effectiveness studies. Overall the choice of studies appears to be reasonable given the need for the data to report non-cirrhotic and cirrhotic patients separately. In the GT1 TN IFN eligible group the source of data for the PEGIFN-2a + RBV treatment was taken from McHutchinson and colleagues.[8] In the appendix describing the MTC a variety of studies in this patient subgroup were reported, of which McHutchinson and colleagues is the largest and therefore likely to be the most reliable source of data (although the MS do not state that this was why McHutchinson and colleagues was chosen). However, the manufacturer's MTC searches identified two other large RCTs; Hadziyannis and colleagues[50] and Roberts and colleagues.[51] The ERG has checked these trials for the SVR in these subgroups and rates appear to be different from those of McHutchinson and colleagues.[8] In the Hadziyannis and colleaguesl[50] trial the SVR in a non-cirrhotic group was approximately 56% (estimated from a figure) and in a cirrhotic group was approximately 38%. In the Roberts and colleagues[51] trial the SVRs were 55% and 24% for the two groups respectively. Alternative SVR estimates for PEG2a+RBV in a GT1 treatment naive population are examined by the ERG in additional analyses given in section 4.3.

The SVR rates reported for telaprevir are correct with the source and the ERG has not identified any alternative estimates in these subgroups. The SVR rates for boceprevir are reported in the MS to come from an unpublished abstract, however, the abstract made available to the ERG did not report these data. The ERG has identified the data in another publication by the same author.[46] In the GT4/5/6 treatment naive subgroup the MS reports (in Table 55) that estimates for PEGI2a+RBV come from Manns and colleagues.[49] This study is an RCT but the numbers in this subgroup are very small and the MS make an assumption that the increase in SVR between fibrosis/cirrhosis and no/minimal fibrosis is the same across genotypes 1, 2/3 and 4/5/6 as no data according to these subgroups were reported in the RCT. Caution is therefore recommended as the ERG was unable to source any alternative data.

The MS does not report the values assumed in the economic model for SVR in an HIV co-infected population. These are given in Table 21 which shows that SVRs for sofosbuvir are drawn from the Phase 3 PHOTON-1 trial and are generally lower than the SVRs given in Table 20 for mono-infected populations. The MS argues that SVRs are similar between mono-infected and co-infected populations (MS p. 168) and uses this as justification to not split out results for the co-infected subgroup in the main economic analysis.

The ERG does not agree that the SVRs for sofosbuvir are similar as, for example, the SVR achieved with SOF+RBV (24 weeks) for non-cirrhotic HCV genotype 1 treatment naive patients co-infected with HIV is 77.1 (Table 21) whilst the corresponding SVR for the mono-infected population is 67.6 (Table 20); and the SVR for HCV genotype 3 treatment naive (SOF+RBV 12 weeks) is 66.7 for HIV co-infected (Table 21) compared with 93.5 for mono-infected (SOF+RBV 24 weeks) (Table 20). On this basis the ERG considers that results for the HCV/HIV co-infected subgroup should have been reported separately in the main economic analysis and not only presented as an appendix. Model outputs given in the MS show that sofosbuvir is not cost-effective in any of the fully incremental analyses in the HCV/HIV co-infected population (Table 16).

Table 21 Summary of genotype-specific SVR rates (%) applied in the economic model for the HCV/HIV co-infected population

Treatment	Treatment duration (weeks)	SVR (%) for non-cirrhotic	SVR (%) for cirrhotic	SVR-12 or SVR-24	Source
HCV genotype 1 treatment-naïve HCV/HIV co-infected					
SOF+RBV	24	77.1	60.0	SVR-12	PHOTON 1
PEG2a+RBV	48	35.2	25.0	SVR-24	Labarga et al 2012[52] (PERICO)
No treatment		0	0		
HCV genotype 2 treatment-naïve HCV/HIV co-infected					
SOF+RBV	12	88.0	100.0	SVR-12	PHOTON 1
PEG2a+RBV	48	86.0	61.1	SVR-24	Labarga et al 2012[52] (PERICO)
HCV genotype 2 treatment experienced HCV/HIV co-infected					
SOF+RBV	12	92.3	100.0	SVR-12	PHOTON 1
PEG2a+RBV	48	86.0	61.1	SVR-24	Labarga et al 2012[52] (PERICO)
No treatment		0	0		
HCV genotype 3 treatment-naïve HCV/HIV co-infected					
SOF+RBV	12	66.7	66.7	SVR-12	PHOTON 1
PEG2a+RBV	48	86.0	61.1	SVR-24	Labarga et al 2012[52] (PERICO)
HCV genotype 3 treatment experienced HCV/HIV co-infected					
SOF+RBV	24	100.0	80.0	SVR-12	PHOTON 1
PEG2a+RBV	48	86.0	61.1	SVR-24	Labarga et al 2012[52] (PERICO)
No treatment		0	0		

Treatment duration is a further clinical event affected by the intervention. The economic model uses the average treatment duration achieved in the relevant trials, or information from the literature where this was not available, in order to estimate the drug acquisition costs and monitoring costs whilst on treatment (MS p.178). The average treatment duration is calculated as the weighted average of the indicated treatment duration for each treatment multiplied by the proportion achieving these duration. These figures are given in MS Tables 45 to Table 55 (MS p. 185-205).

SVR is an intermediate outcome and is related to survival in the model using transition probabilities for disease progression. The key disease progression probabilities used in the model are given in Table 22. The model assumes the same probabilities for all HCV genotypes with the exception of the transition from non-cirrhotic to compensated cirrhosis which is differentiated between HCV genotype 1 and other genotypes.

Table 22 Key generic transition probabilities used in the economic model (extracted and modified from MS Table 44 p182)

Variable	Annual transition probability	Source
Non-cirrhotic to compensated cirrhosis	**Mono-infected** HCV genotype 1: 30 years: 0.006 40 years: 0.010 50 years: 0.016 HCV genotype non-1: 30 years: 0.009 40 years: 0.014 50 years: 0.025 **Co-infected** HCV genotype 1: 30 years: 0.021 40 years: 0.016 50 years: 0.014 HCV genotype non-1: 30 years: 0.096 40 years: 0.061 50 years: 0.041	**Mono-infected** Thomson et al 2008[53] (used by Grishchenko et al 2009[54]) **Co-infected** Thein et al 2008[55]
Non-cirrhotic, SVR to: • non-cirrhotic, recurrence • non-cirrhotic, re-infection	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion, based on the assumption that 1% of patients experience recurrence or reinfection
Compensated cirrhosis to: • decompensated	0.039 0.014	Fattovich et al 1997[56] (used by Wright et al 2006[41] and Hartwell et al 2011[42])

cirrhosis • HCC		
Compensated cirrhosis, SVR to: • Compensated cirrhosis, recurrence • Compensated cirrhosis, re-infection	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion
Decompensated cirrhosis to: • HCC • Liver transplant • Death	 0.014 0.03 0.13	Fattovich et al 1997[56] (used by Wright et al 2006[41] and Hartwell et al 2011[42])
HCC to liver transplant	Base case: 0 Min: 0 Max: 0.01	External expert opinion
HCC to death	0.43	Fattovich et al 1997[56] (used by Wright et al 2006[41] and Hartwell et al 2011[42])
Liver transplant to death, Year 1	0.21	Shepherd et al 2007[43]
Post-liver transplant to death, Year 2	0.057	Shepherd et al 2007[43]

In addition to differentiation by genotype, the transition from non-cirrhotic to compensated cirrhosis is also differentiated by age at treatment (Table 22). This is as supplied in the source publication[54] but the ERG notes that the starting age in the economic model base cases is either 40 or 45 (MS Table 44, p. 182). Consequently only the probability at age 40 years has any bearing on the model outcomes.

The source of the probabilities for the transition from non-cirrhotic to compensated cirrhosis is a study by Grishchenko and colleagues.[54] Previous HTA studies used different probabilities for this transition, based upon the work of Wright and colleagues.[41] The Grischenko and colleagues study is based upon a large (n=315) representative sample of UK cases and centres and provides transition probabilities by three ages at treatment. Probabilities used in previous HTA studies are based upon an age of 25 at infection.[41-43] Given that the age at treatment is assumed to be 45 in the model base case the ERG considers that use of the Grishchenko and

colleagues probabilities is appropriate. These probabilities are moreover slightly lower than the probabilities given by Wright and colleagues[41] which is conservative for model outcomes, i.e. SOF appears less cost-effective with lower probabilities at this transition (section 4.2.9).

The transition probabilities from non-cirrhotic to compensated cirrhosis are given in the source publication as separate probabilities for the transitions from mild cirrhosis to moderate cirrhosis, and from moderate cirrhosis to compensated cirrhosis.[54] The MS describes how Solver optimisation software within Excel was used to obtain the equivalent transition probabilities using only non-cirrhotic and cirrhotic health states (MS p. 179). The ERG notes that an analytical conversion of transition probabilities from three starting states to two starting states is possible if it is assumed that progression times for this transition are exponentially distributed. However based upon the source probabilities given in Grishchenko and colleagues[54] the values given in Table 22 appear reasonable.

The MS does not provide the transition probabilities from the non-cirrhotic to compensated cirrhosis health states which are used for HIV co-infected patients. These are given in Table 22 (figures obtained from Excel model) and are drawn from a study by Thein and colleagues.[55] The MS does not justify the use of these values or indicate how they were calculated using the information supplied by Thein and colleagues.[55] However they are higher than the transition probabilities used for the mono-infected population which has both face validity and is consistent with Thein and colleagues' general findings.[55]

The annual probabilities of moving from non-cirrhotic SVR and cirrhotic SVR to recurrence and re-infection are based on external expert opinion (Table 22). Clinical advice to the ERG agrees that the value used for these probabilities (0.01 in scenario analysis) is reasonable. The probability of obtaining a liver transplant whilst in the HCC state is also based on external expert opinion (Table 22).

The two probabilities of moving from compensated cirrhosis to decompensated cirrhosis, and from compensated cirrhosis to HCC, were obtained from Fattovich and colleagues.[56] The MS states that these probabilities were also used by Wright and colleagues[41] and the previous HTA assessments of Hartwell and colleagues[42] and Shepherd and colleagues[43] (Table 22). The transition probabilities of moving from decompensated cirrhosis to HCC, liver transplant and death, and the probability of death whilst in the HCC state, were also obtained from Fattovitch

and colleagues[56] (MS Table 44, p. 184). The ERG notes however that the probability of moving from decompensated cirrhosis to liver transplant is in fact originally drawn from a study by Siebert and colleagues[57] and that the probability here should be 0.02 rather than 0.03 as given in MS Table 44 and Table 22 below. This inconsistency is conservative as sofosbuvir becomes slightly more cost-effective when a value of 0.02 is used, but does not substantively affect model results.

The value used for the transition from the decompensated cirrhosis state to liver transplant also appears to make the tacit assumption that all patients in the decompensated state are transplant candidates. Clinical advice to the ERG is that patients who are too old, or with certain comorbidities, are not transplant candidates. However the model is not sensitive to the transition probability used here (section 4.2.9) and the ERG feels that this is an acceptable simplifying assumption.

The probabilities of death in the first and subsequent years after liver transplant are obtained from the previous HTA assessment of Shepherd and colleagues.[43] These probabilities are all constant by age which is consistent with previous economic evaluations and HTAs (MS p. 179).

The probability of death by age is obtained from ONS (2011).[58] This is calculated in ten year age bands as the average of male and female mortality (MS p. 184). It is unclear why a weighted average was not used in order to reflect the population likely to be seen in clinical practice (which has a greater proportion of males than females). Alternative weighted mortality probabilities are considered by the ERG in additional work described in section 4.3.

The health effects of adverse events associated with sofosbuvir enter the economic model as incidences. The MS states that rates of grade 3 and 4 pruritus, diarrhoea and nausea, vomiting, rash, anaemia, thrombocytopenia, neutropenia, and depression from the key trials were incorporated into the model. Drug acquisition costs were assigned for interventions associated with managing these side effects (MS p. 179). The MS states that the phase 3 trials were designed to primarily assess clinical efficacy and hence a full systematic review for adverse events was not undertaken (MS p. 149). Sources of the adverse event data used in the model are given in Table 23.

Table 23 Sources of adverse event data used in economic model, by indication (extracted from MS Tables 45 to 55)

Indication	Source
GT1 treatment naïve, interferon eligible	SOF+PEG2a+RBV: NEUTRINO; PEG2a+RBV: Kauffman et al 2011;[59] FDA, 2011;[60] Telaprevir: Kauffman et al 2011;[59] FDA, 2011;[60] Cacoub et al 2012;[61] Bocepravir: Poordad et al 2011.[62] Sources are as identified in footnote g of MS Table 45, MS p.188.
GT1 treatment naïve, interferon ineligible	VALENCE (as the required breakdown was not available from QUANTUM)
GT2 treatment naïve, interferon eligible	VALENCE and FISSION
GT2 treatment naïve, interferon ineligible	VALENCE and POSITRON
GT2 treatment experienced, interferon eligible	VALENCE, FUSION and FISSION
GT2 treatment experienced, interferon ineligible	VALENCE and POSITRON
GT3 treatment naïve, interferon eligible	NEUTRINO, VALENCE and FISSION
GT3 treatment naïve, interferon ineligible	VALENCE
GT3 treatment experienced, interferon eligible	NEUTRINO, VALENCE and FISSION
GT3 treatment experienced, interferon ineligible	VALENCE
GT 4/5/6 treatment naïve	NEUTRINO (SOF+PEG2a+RBV assumed the same as for GT1) and FISSION

GT: genotype

In summary the SVR estimates used in the model are in many cases not robust as they are drawn from single arms of RCTs, non-RCTs and small subgroup analyses. Other transition probabilities are generally reasonable. The MS does not justify its assertion that the SVRs seen in the key trials for mono-infected and HIV co-infected populations are similar.

4.2.5 Patient outcomes

The cost-effectiveness model incorporates the impact of the different treatments on HRQoL as utilities. Utilities are associated with the different health states in the model (see Table 24 below), and in addition the adverse impact of treatment is accounted for by applying utility decrements. The measurement of health benefits in the model is consistent with previous models undertaken in HCV (see Table 24).

A systematic search for HRQoL evidence was undertaken (see section 3.1 for a critique of the search strategy) and is presented in MS Appendix 10.12. Fifty-five studies were identified and

tabulated (MS p. 244-287) but none of these are used for the utility estimates as the MS states (p. 212) that none were deemed more appropriate than the two latest HTA reports (Hartwell and colleagues[42] and Shepherd and colleagues[43]). No other discussion is made about the selection of studies and there is no synthesis of the findings of the review.

For health state utilities the model applies the same utilities for all indications and these are taken from EQ-5D scores. The MS does not report what preference set was used to value the EQ-5D scores. However, as these were based on previously generated utilities it is likely these are valued by a relevant population. The baseline health states of non-cirrhosis and compensated cirrhosis have utilities of 0.74 and 0.55 respectively (MS Table 57, p. 214). Utilities are also applied for all other health states (SVR, DCC, HCC, liver transplant, post-liver transplant; see MS Table 57, p. 214). Estimates of utility for health states were taken from one source (Wright al.,[41]). These have been used in other HTAs in chronic hepatitis C (as summarised in MS Table 57, p. 214).

Treatment-related utilities are then applied using utility decrements which differ depending on treatment (Table 56, p. 214). Estimates of utility for treatment effects were identified in the HRQoL systematic review and were taken from the clinical studies for sofosbuvir, from Wright and colleagues[41] for PEG2a+RBV, and NICE technology appraisals for telaprevir[63] and boceprevir.[64] For treatment-related utilities, for sofosbuvir the SF-36 was used in the trials and this was converted to the SF-6D. The SF-36 was converted to SF-6D utility data for the base case analysis using the method by Brazier and colleagues.[65] The MS states (MS p. 211) that the SF-6D was used in preference to the EQ-5D because the conversion method is well validated and that EQ-5D utilities are less certain. No details of the mapped SF-6D are reported. The estimates for sofosbuvir were taken from the individual clinical trials rather than pooled across all patients. The utility decrements therefore differ according to the genotype group (range from [redacted]). In response to a clarification request the manufacturer re-ran the model applying a pooled estimate (-8%) of the utility decrement due to adverse events from all the relevant trials. This was calculated from an individual patient data analysis. The model results did not alter significantly (see NICE committee papers for full clarification response). A sensitivity analysis was also undertaken using mapped data from the SF-6D to the EQ-5D. Several mapping approaches were used and the final mapping was based on the method described by Gray and colleagues.[66] The MS does not discuss why it did not map the SF-36 scores directly to the EQ-5D. For the comparators the source for utility data for the treatment

utility decrement was not stated (see MS Table 56, p. 212-213) but given the sources reported the ERG has assumed the source was the EQ-5D.

Overall, the ERG view is that the health benefits were measured, and likely to be valued, as per the NICE reference case. The ERG has checked the utilities presented by the MS for the health states against the sources and these are correct.

Table 24 Baseline health state utilities and sources

Health-state	Utility	Source
Baseline – non-cirrhotic	0.74	Wright et al 2006[41]
Baseline – compensated cirrhosis	0.55	Wright et al 2006[41]
SVR (utility increment)	0.05	Wright et al 2006[41]
After treatment at non-cirrhotic stage	0.79	Calculation
After treatment at cirrhotic stage	0.60	Calculation
Decompensated cirrhosis	0.45	Wright et al 2006[41]
Hepatocellular carcinoma	0.45	Wright et al 2006[41]
Liver transplant	0.45	Wright et al 2006[41]
Post-liver transplant	0.67	Wright et al 2006[41]

4.2.6 Resource use

The manufacturer undertook a systematic review of relevant resource data, which is reported in MS appendix 10.13.5. Studies that reported resources and costs specific to the UK were selected and complemented with additional studies identified in two previous HTAs. The MS does not define how the selection of studies was made (with the exception of health state costs which MS page 29 states were based on UK studies) or how the identified studies were applicable to UK clinical practice. No quality assessment appears to have been undertaken.

The MS does not explicitly document the choice of resources for drug acquisition that were appropriate to the model. The MS does not explicitly state assumptions over dosing, frequency, or location of treatments that underlie the acquisition costs of the intervention or comparators. In the Excel model the dosing of sofosbuvir is 400mg per day. RBV is 1200 mg/day (although this varies by mean weight); PEG2a is 180 µg/week; boceprevir is 2400 mg/day and telaprevir is 2250 mg/day. Although no explicit assumptions were provided for the resource use, the doses

used in the model appear to be consistent with those in the trials supporting the clinical effectiveness and the ERG clinical advisors agree that these are used in current clinical practice.

While there is no explicit documentation of the choice of resources for on-treatment monitoring and management of HCV, the resources used are presented in units or % of patients by category in MS appendix 10.14.1. The MS tabulates the detailed costs of a new patient with confirmed HCV (MS Appendix Table 61, p. 299), further investigations (MS Appendix Table 62, p. 300), monitoring during active treatment on sofosbuvir (MS Appendix Table 63, p. 301) and comparators (MS Appendix Table 64, p. 302-305), supplementary monitoring for 48 weeks treatment (MS Appendix Table 65, p. 305-306) and surveillance of interferon ineligible patients (MS Appendix Table 66, p. 306).

Resource use associated with health states is not explicitly reported. MS Appendix 10.13.5 tabulates health state costs for the model used in various studies identified from the systematic literature review and recent HTAs and resources appear to cover all relevant resources. The sources of estimates were taken from three publications (Wright and colleagues;[41] Grishenko and colleagues;[54] Longworth and colleagues[67]). No expert opinion appears to have been used.

Overall, although the MS was not explicit in the choice of resources relevant to the modelling approach, these can be ascertained from various tables presented in the MS and appendices and the estimates appear to cover all relevant resource use. The ERG is unable to confirm whether the population in the model matches the population for which the resource use was estimated. No comprehensive estimate of resource use appears to have been developed separately from the exercise of costing resource use.

4.2.7 Costs

The cost analysis was conducted from an NHS and PSS perspective and drug costs, monitoring costs, disease progression costs and adverse event costs were incorporated into the model. The NHS reference costs used are consistent with previous NICE assessments. A systematic review was conducted to identify the relevant resource data for the UK and the findings are presented in MS Appendix 10.13.5. Two experts were asked to assess the monitoring and treatment of grade 3 and 4 adverse events and the results were validated with two advisory boards with approximately 8 clinical experts on each (MS p. 181).

Costs for the different health states were applied in the model (see MS Table 59, p. 221) and based on results of the systematic review for resources (see also MS appendix 10.13.5) for all health state costs identified. The MS does not describe how choices were made between the studies identified and those selected as appropriate. On-treatment monitoring costs were based on a micro-costing approach and are presented in MS Table 60 (MS p. 222-224). The resource use is taken from PSSRU unit costs 2012 and a previous HTA (Shepherd and colleagues[43]) and inflated to 2011-12 if current costs were unavailable (using the HCHS Pay and Prices index[68]). Unit costs of drugs were taken from the BNF June 2013[69] (MS reference 187).

Drug acquisition costs

The unit costs for sofosbuvir are stated to come from the manufacturer (Gilead) and are presented in MS Table 58 (MS p. 220) and summarised here in Table 25. MS Table 58 also presents the comparator unit costs which are sourced from the BNF 2013.[69] For RBV the MS states that Copegus® was used instead of Rebetol® as it is the cheaper of the available RBV formulations and the ERG agrees that this is reasonable. The cost of sofosbuvir per pack is reported in MS Table 58 (MS p. 220) as £416.46, based on a 400mg dose. The cost per patient over the time frame of the model is £34,504 for 11.84 weeks of treatment (based on the average treatment duration for the HCV genotype 1 treatment naive interferon eligible group). The MS does not state the treatment duration used to calculate the treatment costs and this differs slightly in cases from the recommended treatment duration. Drug acquisition costs for comparators are shown in Table 25.

Table 25 Treatment unit costs

Drug	Cost per pack	Unit dose	Quantity/ pack	Source	Cost over time frame[a]
Sofosbuvir	£416.46	400 mg	1	Gilead	£34,504
RBV	£246.65	400 mg	56	BNF, June 2013[69]	£1,095
PEG2a	£124.40	180 µg	1	BNF, June 2013[69]	£1,472
Telaprevir	£1,866.50	375 mg	42	BNF, June 2013[69]	£22,461
Boceprevir	£2,800.00	200 mg	336	BNF, June 2013[69]	£18,978

[a]based on the average treatment duration in the model for the HCV genotype 1, treatment naive, interferon eligible group

Health state costs

Costs were identified for the health states in the model using published sources taken from the resource/costs systematic review. The costs for the non-cirrhotic health state was based on a calculation of the costs associated previously with mild and moderate HCV (Wright and colleagues[41]) using an assumed 77/23 split between mild and moderate. Costs were inflated to 2011-12 (using the HCHS Pay and Prices index[68]). The key health state costs have been reproduced in Table 26 below. These have been checked by the ERG with the sources. The cited sources of costs are generally old; however, these are consistent with previous NICE appraisals. For the cost of liver transplant the ERG has identified a more recent source with a much lower cost of £18,019 from National Reference costs 2011/12.[70] However, changing this in the cost effectiveness model has only a negligible impact on the model results.

Table 26 Key health state costs

Health state	Annual inflated costs	Source
Non-cirrhotic, no treatment	£367	Calculation based on mild and moderate chronic hepatitis C in Wright et al 2006[41]
Non-cirrhotic, SVR	£243	Calculation based on mild and moderate chronic hepatitis C in Grishchenko et al 2009[54]
Compensated cirrhosis, no treatment	£1,521	Wright et al 2006[41]
Compensated cirrhosis, SVR	£500	Grishchenko et al 2009[54]
Decompensated cirrhosis	£12,193	Wright et al 2006[41]
HCC	£10,865	Wright et al 2006[41]
Liver transplant	£52,768	Longworth et al 2001[67]
Post-liver transplant		
Follow-up phase (0-12 months)	£12,645	Longworth et al 2001[67]
Follow-up phase (12-24 months)	£1,852	Longworth et al 2001[67]

Monitoring costs

A range of monitoring costs was included in the MS, as reported in MS Table 60 (MS p.222-224). These included resource unit costs of outpatient appointments, inpatient care, tests and investigations (virology, chemical pathology, haematology, immunology/chemistry, radiology, molecular pathology, other tests) and procedures (for example liver biopsy). The source for monitoring costs (see MS Table 60, p. 222-224) was the National Schedule of Reference

Costs,[70] or was taken from Shepherd and colleagues,[43] Stevenson and colleagues,[71] Wright and colleagues[41] or expert opinion. Limited detail is provided about how the external expert opinion was obtained. The MS then reports the total costs of the monitoring phases for non-cirrhotic and compensated cirrhotic patients for sofosbuvir and each of the comparator treatments in Table 61 (MS p.225-226) according to the duration of treatment (24 or 48 weeks). MS Table 62 (MS p. 227-228), reports the summary cost of monitoring by genotype, treatment history and PEG eligibility by the baseline health states of non-cirrhotic and compensated cirrhosis.

The MS notes in a footnote to Table 62 that evidence from a single UK centre supports the view that the management costs of triple therapy with the protease inhibitors was estimated to be up to six times higher than reported in previous HTA submissions. However the MS reports the costs from the HTA submissions.

Adverse event costs

Adverse event costs include the costs of various drugs used to treat adverse events (Table 63, MS p. 229) which were sourced from the BNF 2013[69] or the National Schedule of reference costs.[70] Table 64 (MS p. 230) tabulates the resource use of these drugs and the sources used to support these. For nausea, vomiting, diarrhoea, pruritis, and rash the source was the previous telaprevir HTA report. Anaemia, blood transfusion for anaemia, thrombocytopenia, neutropenia and depression were reported to have been sourced from either assumptions, or the BNF. Tables 65-67 (MS p. 231-33) report the outpatient, GP and specialist resources and costs applied for each adverse event. In most cases these were based on expert opinion. The model does not include the costs for any inpatient episodes as a result of adverse events as per the opinion of the experts consulted by the manufacturer.

Assessment of uncertainty

Resource and cost estimates that were subject to sensitivity analyses included the costs for sofosbuvir (varied based on assumption from £313 to £521); monitoring costs for the non-cirrhotic disease SVR state (monitoring and no monitoring), and health state costs (rates either ranged between 0% and 25% or based on the 95% CI of the distribution used for the PSA). The costs of sofosbuvir and comparator treatments were subject to variation in the PSA.

Overall the ERG note that the approach to valuing the resource use is consistent with the NICE reference case. Values are indexed to the current price year and the approach used to uprate published estimates was reported.

4.2.8 Consistency/ Model validation

Internal consistency

The MS reports that two quality assessments of the model were made to assess its internal consistency (MS p. 298). The first was conducted by a senior modeller and a senior statistician with previous experience in chronic hepatitis C. The second check was made by a second modeller not familiar with the project (MS p. 298).

The ERG found one input error in the model for HCV genotypes 4/5/6. In this indication the model uses the probability entered for HCV genotype 1 to inform the transition from non-cirrhotic to compensated cirrhosis at age 40 years, rather than the corresponding probability for non-genotype 1.

External consistency

The model was externally validated with one clinical expert from England (MS p.298). The MS describes an initial meeting with the expert which covered: model structure and underlying assumptions; best clinical data to use for the comparator treatments based on available literature; resource use during treatment and treatment pattern; and adequacy of health state costs obtained from the literature. The MS also states that a final meeting occurred after the model was developed to review the model inputs and results and incorporate any comments/suggestions (MS p. 298).

As a further validation check the MS notes that the proportions of patients reaching SVR predicted by the model are very similar to the corresponding outcomes reported from clinical trials. Tables summarising the SVR rates obtained from the clinical trials and predicted by the model for each comparator by indication are presented in appendix (section 10.14.6) (MS p. 241). The ERG considers that this is an internal validation check since the SVR rates obtained from the clinical trials are used as an input to the economic model and only a fault in model wiring or input data would cause deviation of the model output value from the value seen in the relevant trial. The ERG also notes that the SVR rates presented in section 10.14.6 correspond to the weighted average of the SVR rates for non-cirrhotic and cirrhotic patients and are not broken down by cirrhotic status as might be readily supplied by the model; this would have been a more thorough validation check.

The ERG does not feel that the model has been well validated against external data. As a further external validation check the ERG compares the total costs and QALYs predicted by the model for the GT1 treatment naive, interferon eligible indication with the corresponding figures for PEG2a+RBV, boceprevir and telaprevir obtained from the NICE STAs for boceprevir[1] and telaprevir.[2] These figures are given in Table 27.

Table 27. Comparison of total costs and QALYs obtained from NICE STAs for boceprevir and telaprevir with sofosbuvir economic model outputs (HCV genotype 1, treatment naive, interferon eligible)

	Figures from relevant STAs		Figures from this submission (MS Table 82, p. 248)	
	Total costs (£)	**QALYs**	**Total costs (£)**	**QALYs**
Boceprevir STA[1]				
PEG+RBV	22,128	14.38	24,994	13.8
Boceprevir	32,699	15.30	39,221	14.4
Telaprevir STA[2]				
PEG+RBV	24,722	13.03	24,994	13.8
Telaprevir	36,152	13.87	38,835	14.6

Table 27 indicates that total costs obtained from the sofosbuvir economic model are somewhat higher than the base case costs in the boceprevir STA base case, and that the total telaprevir STA costs are similar. The boceprevir arm costs are around £6,500 higher in the sofosbuvir model than in the boceprevir STA model. This is a relatively large discrepancy, although the fact that the telaprevir and PEG+RBV total costs are more similar between the respective models suggests that the boceprevir total cost difference is driven more by different approaches to costing of this treatment between the two models rather than differences in model structure. The ERG notes that a small part of the total cost difference may arise as the sofosbuvir model assumes that boceprevir is administered solely with PEG2b, which is more costly than PEG2a. This is examined by the ERG in scenario analysis described in section 4.3.

The total QALYs estimated by the sofosbuvir economic model are higher than the QALYs estimated in the telaprevir STA for both PEG+RBV and telaprevir, with differential QALYs of 0.77 and 0.73 respectively. The total QALYs estimated by the sofosbuvir economic model are lower than the QALYs estimated in the boceprevir STA for both PEG+RBV and boceprevir, with differential QALYs of -0.58 and -0.9 respectively.

The sofosbuvir economic model thus makes boceprevir appear less cost effective compared to PEG+RBV than suggested in the boceprevir STA (ICER of £23,712/QALY compared to £11,490/QALY using boceprevir STA figures). The ICERs for telaprevir compared to PEG+RBV are more similar between the sofosbuvir model and the telaprevir STA base case (ICER of £17,301/QALY compared to £13,607/QALY using telaprevir STA figures).

In summary the sofosbuvir model is broadly consistent with previous STAs in terms of PEG+RBV total costs and QALYs, and with telaprevir total costs and QALYs. There is a relatively large discrepancy between models in boceprevir total costs. The ERG does not have access to the data used in the boceprevir submission and so was unable to check in detail for potential causes of this difference.

4.2.9 Assessment of Uncertainty

One-way sensitivity analyses

The MS reports 15 sets of DSA results for the 15 comparisons considered in the main economic analysis.

41 one-way sensitivity analyses which are common to all comparisons are reported in MS Table 68 (MS p. 235). Indication-specific input ranges are given in MS appendix 10.14.1 (p. 307). In some cases groups of variables were varied together rather than individually. These are identified on MS p. 234.

Ranges are clearly stated. In many cases the range is given by ± 25% of the mean value although this is not justified. In other cases the range examined is based on the 95% CI of the distribution used for the PSA (which is itself in many cases based on a ± 25% increment to the base case value, e.g. for liver transplant candidacy phase cost). SVR values are drawn from beta distributions which are appropriately parameterised using the numbers of responders and non-responders in the key trials.

Results of the DSA are presented as tornado diagrams (MS p. 253-281). The ERG notes that for some comparisons and parameters the diagrams do not fully represent the uncertainty as the bars do not cross the base case ICER (e.g. MS Figure 23, p. 257). It would have been

preferable to use net monetary benefit as the metric for display on these diagrams, rather than ICER, as it is continuous even when a treatment is dominated or dominates.

Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and utility increment after reaching SVR have a large impact on final ICER in all of the comparisons considered in the DSA. In some comparisons the ICER exceeds £30,000 per QALY. The model also shows sensitivity to the following three variables for some or all of comparisons: SVR-12 sofosbuvir (cirrhotic); transition probability from non-cirrhotic to compensated cirrhosis at age 40 years; the cost per pack of sofosbuvir; and the costs of non-cirrhotic disease.

The MS concludes from the DSA that at a £20,000/QALY threshold sofosbuvir continues to be cost-effective in all scenarios in the following patient populations (MS p. 296):

- HCV genotype 2 treatment-naïve and treatment experienced unsuitable for interferon (compared against no treatment)
- HCV genotype 2 and 3 treatment experienced, interferon eligible (compared against no treatment)

Variation to the most influential variables produces ICERs slightly over £20,000/QALY in the following patient populations (MS p296):

- HCV genotype 1 treatment naïve, interferon eligible (compared against PEG2a+RBV and against boceprevir+PEG2b+RBV)
- HCV genotype 2 treatment experienced, interferon eligible (compared against no treatment or PEG2a+RBV)
- HCV genotype 3 treatment experienced, interferon eligible (compared against no treatment or PEG2a+RBV)

Variation to the most influential variables produces ICERs slightly over £30,000/QALY in the following patient populations (MS p297):

- HCV genotype 1 treatment naïve, interferon eligible (compared against telaprevir+PEG2a+RBV)

- HCV genotype 3 treatment naïve, unsuitable for interferon (compared against no treatment)
- HCV genotype 3 treatment naïve, interferon eligible (compared against PEG2a+RBV)

The manufacturer also reports DSA for those genotype subgroups which were not cost effective at £30,000 per QALY in the base case analysis. The ERG agrees with the MS conclusions from DSA. In addition there is a further indication that is not cost-effective at £30,000/QALY although it is cost-effective at this threshold in the base case (MS Figure 35 p. 231):

- Genotype 4/5/6 treatment naive, interferon-eligible (compared against PEG+RBV)

The ERG also notes that although the main economic analysis reports 15 sets of DSA results corresponding to the comparisons presented in the main economic analysis, more indications are permitted in the economic model. However DSA results for these are not supplied in the MS.

Scenario Analysis

The MS reports several scenario analyses which were undertaken and reported as part of the DSA. The scenarios examined are the possibility of reinfection and recurrence post SVR; and the probability of liver transplant from the HCC state. Alternative parameter values were obtained from expert opinion (MS Table 68 p. 235). Clinical advice to the ERG agreed that these values are appropriate.

The MS concludes from these analyses that the economic results are not sensitive to these structural changes (MS p. 296). The ERG agrees with this assessment.

Probabilistic Sensitivity Analysis

The MS reports results from PSA with 1000 iterations for each of the indications and comparator considered in the base case (MS section 7.7.8, p.282). For each indication and comparator the MS reports the probabilities that sofosbuvir will be cost-effective at the thresholds of £20,000 and £30,000 per QALY. The mean costs, QALYs and ICER arising from the PSA runs are not reported. The ERG re-ran the PSA with 1000 iterations and found that it takes approximately 30 seconds to run.

Distributions used in PSA for parameters general to all indications are given in MS Table 69 (MS p. 238). Distributions for indication-specific parameters are given in MS appendix 10.14.1. The MS does not indicate the source of the data or the method used to calculate the distribution parameters. However data sources are supplied in the model spreadsheet for most parameters.

Notwithstanding the lack of documentation the ERG considers that the methods of assessment of parameter uncertainty are appropriate and that the distributions are correctly applied. Mean estimates given in MS Table 69 (MS p. 238) and appendix 10.14.1 are appropriate. Correlation between parameters is not explored as none is assumed. The ERG believes that this is a satisfactory approach.

The ERG re-ran the PSA results for all comparisons considered in the base case as it found a slight error in the settings of the slider control used to set the probability of cost-effectiveness at the £20,000 and £30,000 WTP thresholds. This error is indicated in all of the cost effectiveness acceptability curves (CEACs) given in the MS (e.g. Figure 37, MS p. 282) where the line drawn at the £20,000 threshold is not at exactly £20,000, but a little below. Thus other things being equal sofosbuvir has a higher probability of being cost-effective at the two WTP thresholds than given in the MS. Results from the ERG analysis are compared with results from the manufacturer's analysis in Table 28 and Table 29.

Table 28 Probability that sofosbuvir is cost-effective at £20,000 per QALY – comparison of MS and ERG results

Indication and comparator	MS probability (approximate) (%)	ERG probability (%)
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT1 TN IFN eligible	63	68
SOF+PEG2a+RBV (12 weeks) versus telaprevir+PEG2a+RBV in GT1 TN IFN eligible	68	69
SOF+PEG2a+RBV (12 weeks) versus boceprevir+PEG2b+RBV (48 weeks) in GT1 TN IFN eligible	85	86
SOF+RBV (24 weeks) versus NT in GT1 TN unsuitable for IFN	<5%	1
SOF+RBV (12 weeks) versus PEG2a+RBV (24 weeks) in GT2 TN IFN eligible	<5%	4
SOF+RBV (12 weeks) versus NT in GT2 TN unsuitable for IFN	98	99

SOF+RBV (12 weeks) versus NT in GT2 TE IFN eligible	95	97
SOF+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT2 TE IFN eligible	78	82
SOF+RBV (12 weeks) versus NT in GT2 TE unsuitable for IFN	97	99
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (24 weeks) in GT3 TN IFN eligible	37	42
SOF+RBV (24 weeks) versus NT in GT3 TN unsuitable for IFN	30	35
SOF+PEG2a+RBV (12 weeks) versus NT in GT3 TE IFN eligible	96	98
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT3 TE IFN eligible	75	80
SOF+RBV (24 weeks) versus NT in GT3 TE unsuitable for IFN	12	14
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT4/5/6 TN	24	26

GT: genotype; IFN, interferon; NT, no treatment; TE, treatment experienced; TN, treatment naive

Table 29 Probability that sofosbuvir is cost-effective at £30,000 per QALY – comparison of MS and ERG results

Indication and comparator	MS probability (approximate) (%)	ERG probability (%)
SOF2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT1 TN IFN eligible	90	94
SOF+PEG2a+RBV (12 weeks) versus telaprevir+PEG2a+RBV in GT1 TN IFN eligible	85	83
SOF+PEG2a+RBV (12 weeks) versus boceprevir+PEG2b+RBV (48 weeks) in GT1 TN IFN eligible	95	96
SOF+RBV (24 weeks) versus NT in GT1 TN unsuitable for IFN	10	10
SOF+RBV (12 weeks) versus PEG2a+RBV (24 weeks) in GT2 TN IFN eligible	10	14
SOF+RBV (12 weeks) versus NT in GT2 TN unsuitable for IFN	100	100
SOF+RBV (12 weeks) versus NT in GT2 TE IFN eligible	100	100
SOF+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT2 TE IFN eligible	95	97
SOF+RBV (12 weeks) versus NT in GT2 TE unsuitable for IFN	100	100
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (24 weeks) in GT3 TN IFN eligible	80	79
SOF+RBV (24 weeks) versus NT in GT3 TN unsuitable for IFN	80	78
SOF+PEG2a+RBV (12 weeks) versus NT in GT3 TE IFN eligible	100	100

SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT3 TE IFN eligible	98	96
SOF+RBV (24 weeks) versus NT in GT3 TE unsuitable for IFN	48	48
SOF+PEG2a+RBV (12 weeks) versus PEG2a+RBV (48 weeks) in GT4/5/6 TN	50	48

GT: genotype; IFN: interferon; NT: no treatment; TE: treatment experienced; TN: treatment naive

The MS does not draw any general conclusions from the results of the PSA. The ERG concludes that at a threshold of £20,000 per QALY sofosbuvir is not cost effective in six of the base case comparisons as it has a probability of cost-effectiveness of less than 50%. These comparisons are shown by the shaded cells in Table 28. At a threshold of £30,000 per QALY sofosbuvir is not cost effective in four of the base case comparisons, as shown by the shaded cells in Table 29.

4.2.10 Comment on validity of results with reference to methodology used

The economic model captures most of the important aspects of the disease pathway. It does not include a transition from the SVR-Cirrhotic health state to the HCC health state but this is shown in additional analyses to not affect cost-effectiveness conclusions substantively (see Section 4.3). The model extrapolates intermediate outcomes to final outcomes in a consistent manner, drawing upon standard sources from the literature.

The model is structured with two initial health states, cirrhotic and non-cirrhotic. SVR estimates in the clinical literature are not commonly supplied using this categorisation and this has led to the use of non-robust data to populate some SVRs in the model.

4.3 Additional work undertaken by the ERG

In addition to the external validation described in section 4.2.8 and additional runs of the PSA described in section 4.2.9, the ERG undertook additional work to:

a) Examine the variation in the final ICER arising with the use of alternative estimates of SVR for PEG2a+RBV in the GT1 treatment naive interferon eligible population.

b) Examine the cost-effectiveness of boceprevir compared to sofosbuvir using PEG2a cost data for boceprevir

c) Examine the effect on the final ICERs of including a transition from SVR-Cirrhotic to the HCC health state

d) Examine the impact of a discount rate of 1.5% for costs and outcomes

e) Assess the effect of variation to all-cause mortality probabilities

f) Verify the manufacturer's exploratory analysis in a GT1 treatment experienced population

g) Assess the effect of using PEG2b and Rebetol costs instead of PEG2a and Copegus costs

a) Alternative estimates of SVR for PEG2a+RBV in HCV genotype 1 treatment naive, interferon eligible population

The MS does not use results of the MTC in the economic model and the ERG generally agrees that this is appropriate. However the ERG notes that there are a number of SVR estimates available in the literature for PEG2a+RBV in the GT1 treatment naive, interferon eligible population but that the manufacturer did not examine these (see section 4.2.4). Given that the SVR estimate for PEG1a+RBV obtained in the MTC is based upon a number of studies the ERG considers that this provides an alternative indication of its efficacy, albeit one that is not differentiated by cirrhotic status. The ERG re-ran the model with the MTC PEG2a+RBV SVR estimate of 46.2% for both cirrhotic and non-cirrhotic patients (MS Table 346) in the GT1 treatment naive, interferon eligible population. Results are given in Table 30. Note that these results are not the same as those of the MS MTC (MS Table 347) as only the MTC SVR estimate for PEG2a was used.

The ERG also re-ran the model for this indication with the alternative SVR estimates for PEG2a+RBV identified in section 4.2.4. Roberts and colleagues[51] give PEG2a+RBV SVR figures of 55% and 24% for non-cirrhotic and cirrhotic respectively. The corresponding SVRs from the Hadziyannis[50] study are 56% and 38%. Model results with these SVRs are given in Table 31 and Table 32.

Table 30. Cost-effectiveness results, HCV genotype 1 treatment naive, interferon eligible using PEG2a+RBV SVR data from the MTC

Technologies	Total costs	Total QALYs	Incre-mental	Incre-mental	ICER vs.	ICER incremental

	(£)		costs (£)	QALYs	baseline (QALYs)	(QALYs)
PEG2a+RBV (48 weeks)	£23,192	14.045	-	-	-	-
Boceprevir+PEG2b+RBV	£39,221	14.419	£16,029	0.374	£42,858	Extended dominance
Telaprevir+PEG2a+RBV	£38,835	14.645	£15,643	0.600	£26,072	Extended dominance
SOF+PEG2a+RBV (12 weeks)	£44,123	15.092	£20,931	1.047	£19,991	£19,991

Table 31. Cost-effectiveness results, HCV genotype 1 treatment naive, interferon eligible using PEG2a+RBV SVR data from Roberts and colleagues[51]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (48 wks)	£23,862	13.979	-	-	-	-
Boceprevir+PEG-IFN-2b+RBV	£39,221	14.419	£15,359	0.440	£34,928	Extended dominance
Telaprevir+PEG-IFN-2a+RBV	£38,835	14.645	£14,973	0.666	£22,491	Extended dominance
SOF+PEG-IFN-2a+RBV (12 wks)	£44,123	15.092	£20,261	1.113	£18,209	£18,209

Table 32. Cost-effectiveness results, HCV genotype 1 treatment naive, interferon eligible using PEG2a+RBV SVR data from Hadziyannis and colleagues[50]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (48 wks)	£22,802	14.116	-	-	-	-
Boceprevir+PEG-IFN-2b+RBV	£39,221	14.419	£16,419	0.303	£54,207	Extended dominance
Telaprevir+PEG-IFN-2a+RBV	£38,835	14.645	£16,033	0.529	£30,314	Extended dominance
SOF+PEG-IFN-2a+RBV (12 wks)	£44,123	15.092	£21,321	0.976	£21,848	£21,848

Table 30 shows that, with the MTC SVR estimate for PEG2a+RBV, the ICER for SOF+PEG2a+RBV compared to PEG2a+RBV rises to £19,991 per QALY compared to the base case ICER of £14,930 per QALY. Thus SOF+PEG2a+RBV remains cost-effective compared to PEG2a+RBV at a WTP of £20,000 per QALY, but marginally so.

The Roberts and colleagues[51] PEG2a+RBV SVR estimates are associated with an ICER of £18,209 per QALY for SOF+PEG2a+RBV compared to PEG2a+RBV, again an increase compared to the base case (Table 31). With the Hadziyannis and colleagues PEG2a+RBV

SVR estimates[50] the ICER for SOF+PEG2a+RBV compared to PEG2a+RBV becomes £21,848 (Table 32), i.e. within this indication SOF+PEG-IFN-2a+RBV is no longer cost-effective compared to PEG2a+RBV at a WTP of £20,000 per QALY.

The ERG note the same caution is required with interpreting these results as arise from interpreting the MS results because the estimates of SVRs are not based on controlled comparator studies or linked through any robust statistical analysis.

b) Total cost and QALY data from boceprevir STA: HCV genotype 1, treatment naive, interferon eligible

The ERG notes in section 4.2.8 that the total cost and total QALY outcomes for boceprevir obtained from the economic model are relatively different from the total cost and QALY figures given in the boceprevir STA base case.[1] Total discounted costs for the boceprevir arm are approximately 20% higher in the sofosbuvir submission than in the boceprevir STA. One possible reason for some of these higher costs is that the sofosbuvir model considers boceprevir in combination with PEG2b rather than in combination with PEG2a.

The ERG has re-run the model using PEG2a cost data on the boceprevir arm and assuming the same SVRs as the base case. This gives the results shown in Table 33. Boceprevir+PEG-IFN-2a+RBV is subject to extended dominance by SOF+PEG-IFN-2a+RBV as it has a higher ICER compared to the baseline treatment PEG-IFN-2a+RBV. This compares to the base case where boceprevir is dominated by telaprevir as it is more expensive than telaprevir, and associated with fewer QALYs.

Table 33. Cost-effectiveness results, HCV genotype 1 treatment naive interferon eligible using total cost and QALY data from boceprevir STA[1]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (48 wks)	£24,994	13.8	-	-	-	-
Boceprevir+PEG-IFN-2a+RBV	£38,195	14.4	£13,201	0.619	£21,313	Extended dominated
Telaprevir+PEG-IFN-2a+RBV	£38,835	14.6	£13,841	0.845	£16,380	Extended dominated
SOF+PEG-IFN-2a+RBV (12 wks)	£44,123	15.1	£19,129	1.292	£14,806	£14,806

c) Inclusion of transition from SVR-Cirrhotic to HCC state

The manufacturer's model does not include a transition from the SVR-Cirrhotic health state to the HCC health state. This transition was however included in the most recent SHTAC model.[42] Clinical advice to the ERG also indicated that this transition should be included in the sofosbuvir model in order to better reflect the clinical course of the disease. In response to a clarification request from the ERG the manufacturer included this transition in the model and obtained the results given in Table 34.

Table 34. Manufacturer's revised ICERs from model which includes transition from SVR-Cirrhotic to HCC

Indication	Comparison	Submitted ICER (£/QALY)	BC ICER: 0.005 (£/QALY)	LB ICER: 0.002 (£/QALY)	UB ICER: 0.013 (£/QALY)
GT2 TN IE	SOF vs. PEG2a+RBV (24 wks)	46,324	49,617	47,636	54,957
GT2 TN UI	SOF vs. No treatment	8,154	8,694	8,371	9,544
GT2 TE IE	SOF vs. No treatment	9,274	9,825	9,496	10,684
	SOF vs. PEG2a+RBV (48 wks)	12,519	13,189	12,788	14,227
GT2 TE UI	SOF vs. No treatment	8,591	9,149	8,815	10,027
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	22,850	21,489	26,771
GT3 TN UI	SOF vs. No treatment	21,478	23,032	22,096	25,574
GT3 TE IE	SOF vs. No treatment	8,557	9,273	8,842	10,442
	SOF vs. PEG2a+RBV (48 wks)	12,246	13,214	12,631	14,796
GT3 TE UI	SOF vs. No treatment	28,569	30,190	29,219	32,758
GT1 TN IE	SOF vs. telaprevir	11,836	12,743	12,197	14,216
	SOF vs. boceprevir	7,292	7,829	7,507	8,684
	SOF vs. PEG2a+RBV (48 wks)	14,930	16,070	15,384	17,934
GT1 TN UI	SOF vs. No treatment	49,249	51,294	50,074	54,434
GT4/5/6	SOF vs. PEG2a+RBV (48 wks)	26,797	27,468	27,071	28,451

BC: Base case; GT: Genotype; LB: Lower bound; QALY: Quality Adjusted Life Year; SOF: Sofosbuvir; TE: Treatment experienced; TN: Treatment-naïve; UB: Upper bound; UI: Unsuitable for interferon; wks: weeks

The ICERs in Table 34 were produced with the assumption that the annual transition probability from cirrhotic with SVR to HCC is 0.005. This figure is from a study by Cardoso and colleagues.[72] The manufacturer's clarification letter does not supply details of the calculation of this probability from figures given in Cardoso and colleagues[72] and the ERG was unable to reproduce the value of 0.005. The rate of HCC given SVR supplied in Cardoso and colleagues (table 2) is 1.24 per 100 person years[72] which by ERG calculations corresponds to a transition probability of 0.0123 per year. At this probability the ERG notes that base case ICERs will be similar to figures given in the upper bound (UB:0.013) column in Table 34, rather than those given in the base case (BC) column in Table 34. For example for the GT 4/5/6 population the ERG has calculated an ICER of £28,369 per QALY with the revised transition probability of 0.0123, compared to £28,451 per QALY given in the final column of Table 34. For the GT1 treatment naive IFN eligible population versus telaprevir the ERG calculated ICER is £14,086 per QALY, compared with £14,216 per QALY given in Table 34.

d) Discount rate of 1.5%

ICERs for all of the indications examined in the base case are very sensitive to the discount rate that is used for costs and outcomes (section 4.2.9). The MS describes DSA which examines a range in discount rate from 0-6% (MS Table 68 p. 237) and produces tornado diagrams of the outputs (MS p253-281). The NICE Methods Guide advises that sensitivity analyses using discount rates of 1.5% for both costs and health effects may be presented alongside the base case analysis. This is not reported in the MS but is given in Table 35.

Table 35. Revised ICERs with discount rate set to 1.5% for costs and health effects

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT2 TN IE	SOF vs. PEG2a+RBV (24 wks)	46,324	28,120
GT2 TN UI	SOF vs. no treatment	8,154	3,390
GT2 TE IE	SOF vs. no treatment	9,274	4,092
	SOF vs. PEG2a+RBV (48 wks)	12,519	6,356
GT2 TE UI	SOF vs. no treatment	8,591	3,668
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	11,268

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT3 TN UI	SOF vs. no treatment	21,478	11,999
GT3 TE IE	SOF vs. no treatment	8,557	3,678
	SOF vs. PEG2a+RBV (48 wks)	12,246	6,200
GT3 TE UI	SOF vs. no treatment	28,569	16,492
GT1 TN IE	SOF vs. telaprevir	11,836	6,078
	SOF vs. boceprevir	7,292	3,949
	SOF vs. PEG2a+RBV (48 wks)	14,930	8,069
GT1 TN UI	SOF vs. no treatment	49,249	29,726
GT4/5/6	SOF vs. PEG2a+RBV (48 wks)	26,797	16,032

GT: Genotype; IE: Interferon eligible; QALY: Quality Adjusted Life Year; TE: Treatment experienced; TN: Treatment-naïve;; UI: Unsuitable for interferon; wks: weeks

Table 35 shows that all ICERs are reduced appreciably when a discount rate of 1.5% is used. For four comparisons sofosbuvir becomes cost-effective at a WTP threshold of £20,000 per QALY where it was not cost-effective in the base case. These indications are GT3 treatment naïve, interferon eligible; GT3 treatment naïve, unsuitable for interferon; GT3 treatment experienced, unsuitable for interferon; and GT4/5/6. Two indications which were not cost-effective at a WTP threshold of £30,000 in the base case become cost-effective when a discount rate of 1.5% is used. These are GT2 treatment naïve, interferon eligible and GT1 treatment naïve, unsuitable for interferon.

e) Assess the effect of variations to all-cause mortality probabilities

The manufacturer's clarification letter confirms that a simple average of male and female mortality figures was used to calculate the age-specific mortality rates used in the model. The ERG does not feel that this is appropriate as the treatment population seen in English clinical practice is more likely to be male. The manufacturer re-ran the model with weighted average mortality probabilities and obtained the figures given in Table 36.

The manufacturer's clarification letter does not indicate the weights which were used to obtain the clarification ICERs given in Table 36. The ERG re-ran the model assuming a weighting of

61% males/39% females as given in Wright and colleagues[41] and obtained the ICERs given in the final column of Table 36.

Table 36. Revised ICERs with weighted average of all-cause mortality

Indication	Comparison	Submitted ICER	Clarification ICER	ERG ICER
GT2 TN IE	SOF vs. PEG2a+RBV (24 wks)	46,324	46,010	46,909
GT2 TN UI	SOF vs. No treatment	8,154	8,050	8,340
GT2 TE IE	SOF vs. No treatment	9,274	9,159	9,479
	SOF vs. PEG2a+RBV (48 wks)	12,519	12,379	12,770
GT2 TE UI	SOF vs. No treatment	8,591	8,483	8,784
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	20,458	20,900
GT3 TN UI	SOF vs. No treatment	21,478	21,257	21,867
GT3 TE IE	SOF vs. No treatment	8,557	8,452	8,746
	SOF vs. PEG2a+RBV (48 wks)	12,246	12,112	12,488
GT3 TE UI	SOF vs. No treatment	28,569	28,281	29,079
GT1 TN IE	SOF vs. Telaprevir	11,836	11,714	12,057
	SOF vs. Boceprevir	7,292	7,202	7,453
	SOF vs. PEG2a+RBV (48 wks)	14,930	14,778	15,205
GT1 TN UI	SOF vs. No treatment	49,249	48,777	50,083
GT4/5/6	SOF vs. PEG2a+RBV (48 wks)	26,797	26,538	27,265

GT: Genotype; IE: Interferon eligible; QALY: Quality Adjusted Life Year; TE: Treatment experienced; TN: Treatment-naïve;; UI: Unsuitable for interferon; wks: weeks

It may be seen from the table that the clarification ICERs are all lower than the submitted ICERs, while the ERG ICERs are all higher than the submitted ICERs. As noted the manufacturer may have used a different weighting. The ERG ICER is no more than £1,000 higher per QALY than the submitted ICER in all cases.

f) Exploratory analysis in a HCV genotype 1 treatment experienced population

The MS notes that the licence for sofosbuvir covers HCV genotype1 treatment experienced patients due to the high unmet need and lack of suitable treatment (MS p.168). However, no

empirical evidence exists for this indication. In response to a clarification request the manufacturer conducted further analyses and found that SOF+PEG2a+RBV is cost-effective in HCV genotype 1 treatment experienced patients against telaprevir (£8,203/QALY), boceprevir (£683/QALY) and PEG2a+RBV (£12,641/QALY).

The clarification letter gives some detail of the assumptions made in order to obtain these estimates but this is limited in places and the ERG has been unable to reproduce these ICERs. Changing both treatment efficacy and treatment duration as given in the clarification letter, the ERG calculated an ICER of £12,395 per QALY for SOF+PEG2a+RBV to replace PEG2a+RBV in the HCV genotype 1 treatment experienced population. Corresponding ERG-calculated ICERs for telaprevir and boceprevir are £13,214 per QALY and £9,069 per QALY respectively. Whilst these ICERs remain within the £20,000 per QALY WTP threshold they should be considered with caution because of limitations in the evidence base.

g) PEG2b and Rebetol costs used instead of PEG2a and Copegus costs

In line with EASL guidelines the model assumes that PEG2a and PEG2b have the same efficacy, and uses PEG2a to inform treatment costs for all treatments except boceprevir. Whilst PEG2a is given in combination with Copegus ribavirin, PEG2b is given in combination with Rebetol ribavirin.

Given that PEG2b is more expensive than PEG2a, but is nonetheless likely to be used in clinical practice, the ERG has explored the impact of using PEG2b+Rebetol costs in selected indications, with results given in Table 37.

Table 37. Revised ICERs with PEG2b+Rebetol costs*

Indication	Comparison	Submitted ICER	Revised ICER
GT1 TN IE	SOF vs. Telaprevir	11,836	11,490
	SOF vs. Boceprevir	7,292	8,561
	SOF vs. PEG+RBV (48 wks)	14,930	14,748
GT1 TN UI	SOF vs. No treatment	49,249	48,781
GT4/5/6	SOF vs. PEG+RBV (48 wks)	26,797	26,537

* Assumptions: the dose of Rebetol is 1000 mg per day based on an average body weight of 79kg.[43] The cost of Rebetol is £321.38 for 168 200mg tablets.[69] The dose of PEG2b is assumed to be 1.5mcg per kilo

per week, giving 119mcg per week at an assumed body weight of 79kg.[43] The cost of PEG2b is £159.51 for 120mcg.[69]

The ERG notes that the impact of these alternative costs on the final ICER will vary by indication depending upon the assumed PEG treatment duration, and whether PEG is also given in combination with sofosbuvir and/or the comparator. The revised ICERs given in Table 37 are all within £1,000 per QALY of the original base case ICERs demonstrating no substantive change to model outcomes.

4.4 Summary of uncertainties and issues

The economic model structure is a modified version of a model structure used in previous HTA reports to NICE. The model replaces the 'mild', 'moderate' and 'severe' cirrhosis starting health states of previous models with two health states, non-cirrhotic and cirrhotic. Consequently the model requires estimates of proportion achieving SVR for each of these health states but these data are less common in the literature than data for the 'mild', 'moderate' and 'severe' health states. The clinical efficacy data used in the model are thus in many cases not robust.

Some of the model SVR estimates come from single arms of RCTs which were not linked through any statistical methods to one another while others are drawn from non-RCTs and from small subgroup analyses. In instances where multiple efficacy estimates are available for the same treatment and indication (i.e. PEG2a in GT1 treatment naïve interferon eligible patients) the model uses an estimate drawn from one source and does not examine alternative efficacy estimates in sensitivity analysis.

In several cases the ERG was unable to find the efficacy figures or transition probabilities used in the MS in the publications cited in the MS. Other calculations are not presented in sufficient detail in the MS to allow replication.

The model is not well validated against external data. The sofosbuvir economic model results show that bocepravir+PEG2b+RBV is not cost-effective compared to PEG+RBV at a WTP of £20,000 per QALY. This does not agree with findings presented in the boceprevir STA.

5 Innovation

The manufacturer makes the case that sofosbuvir offers a new treatment option across all chronic hepatitis C genotypes and offers a step-change in treatment efficacy, safety and

tolerability (MS p. 48). The MS goes on to argue that sofosbuvir meets the criteria for innovation. Sofosbuvir is a first-in-class oral uridine nucleotide (MS p. 16). The manufacturer outlines the following benefits of sofosbuvir over current standard of care (MS p. 48 – 49):

- no response-guided therapy is needed during treatment
- a shorter treatment duration
- a low risk of viral resistance
- a safe option for liver transplant patients and HIV co-infected patients, as it can be used with immunosuppressant drugs and "commonly used" (MS p. 49) antiretroviral drugs
- the first all orally administered treatment option for individuals unsuitable for interferon

6 DISCUSSION

6.1 Summary of clinical effectiveness issues

The MS appears to have identified all existing clinical studies relevant to the NICE scope. However, the available evidence does not fully address the decision problem because no efficacy or safety data for sofosbuvir are available for HCV genotype 1 treatment experienced patients, a group which currently has unmet treatment needs. Only one RCT provides a head-to-head comparison of sofosbuvir against standard of care (PEG+RBV) as specified in the NICE scope, and this is in a mixed population of patients with HCV genotypes 2 and 3. No studies have directly compared sofosbuvir-based regimens against the protease inhibitors boceprevir or telaprevir as specified in the NICE scope.

A particular issue with the clinical studies is that most studies which included patients with HCV genotypes 2 and 3 included mixed populations of these genotypes. Current licensed indications for sofosbuvir differ between HCV genotypes 2 and 3, meaning that in these studies on mixed-genotype populations only one of the genotypes would have received the appropriate licensed sofosbuvir regimen. In most cases the SVR12 data from the clinical studies that are used to inform the economic model are from HCV genotype-specific subgroups, ensuring consistency with the licensed indications for sofosbuvir. However, a limitation of these HCV genotype-specific subgroups is that they have smaller sample sizes than the starting populations in the studies and the studies' analyses were not powered statistically to detect differences between subgroups. For the purposes of the economic analysis the HCV genotype-specific subgroups were split further according to patients cirrhosis status, which in some cases yielded extremely small sample sizes for the subgroups ($n<5$).

6.2 Summary of cost effectiveness issues

The base case results reported in the MS show that sofosbuvir in combination with other treatments is cost-effective in 9 of the 15 treatment comparisons considered in the base case at a WTP threshold of £20,000 per QALY. These results are confirmed by the CEAC curve arising from PSA at a WTP of £20,000 per QALY (i.e. in six comparisons sofosbuvir has a probability of being cost-effective of less than 50%) and persist also when the model is altered to include a transition from the SVR-Cirrhotic to the HCC state. However in the GT1 treatment naïve interferon eligible indication sofosbuvir is not cost-effective compared to PEG2a+RBV when alternative SVR estimates for PEG2a+RBV are used.

The base case results are generally robust to other model changes examined by the ERG except that sofosbuvir becomes cost-effective at a WTP of £20,000 per QALY in four of the base case treatment comparisons when a discount rate of 1.5% is used (where it was not cost-effective in the base case).

At a WTP threshold of £30,000 per QALY sofosbuvir is not cost-effective in two of the base case treatment comparisons. These results are not wholly reflected in the PSA findings as at a WTP threshold of £30,000 per QALY sofosbuvir has a probability of being cost effective of less than 50% in four comparisons (ERG revised PSA).

SVR estimates used in the model are in many cases not robust. Some are drawn from single arms of RCTs while others are drawn from non-RCTs and small subgroup analyses. SVR estimates in the HIV coinfected population are particularly uncertain. Sofosbuvir was not found to be cost-effective for any treatment comparison in this subgroup.

The model does not appear to have been well-validated against external sources of data.

7 REFERENCES

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