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Economic Analysis to Support NHS Implementation of Hepatitis C Drugs: Scoping Study

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The views expressed in this report are those of the authors and not those of the Department of Health. Any errors are the responsibility of the authors.

Proviso

This report was developed as part of a scoping project for NHS England and the UK Department of Health on the economic analysis that is required to support the implementation of treatments for chronic hepatitis C. Due to the short time frame available to complete the work, it utilises sources of evidence that were immediately available and known to the project team, rather than having conducted a formal review of the evidence. Estimates of costs and other outcomes should not be considered definitive and will be subject to change following further modelling and with a more considered assessment of available data sources. This report is currently under peer-review.

Contents

1 Executive Summary

A number of new treatments for chronic hepatitis C have recently undergone or are currently undergoing appraisal of their value to the National Health Service (NHS) in England and Wales by the National Institute of Health and Care Excellence (NICE): simeprevir, sofosbuvir, ledipasvir-sofosbuvir, daclatasvir and ombitasvir-paritaprevir-ritonavir with or without dasabuvir. These new treatments are an addition to the existing interferon-based therapies: dual therapy with interferon and ribavirin, and triple therapy with boceprevir or telaprevir with interferon and ribavirin. The aim of this work is to provide a basis for decisions about substantive research which could be undertaken to inform NHS decisions about the implementation of NICE guidance on hepatitis C drugs.

The NICE guidance has considered whether, for a given patient at a particular stage in their disease and treatment for hepatitis C, one of the new drugs might provide value. However, the results do not lend themselves to directly inform implementation strategies about prioritising access to new drugs for hepatitis C in a way that maximises health benefits and value to the NHS. As a result, there are four key challenges raised by the NICE guidance in the operationalization of its implementation by NHS England:

1. **No clear guidance on how to prioritise implementation of the range of treatments recommended as options.** The NICE recommendations implicitly include watchful waiting and treatment sequencing strategies given the different recommendations by disease severity and prior treatment experience. The lack of direct comparison between these strategies and a 'treat all' strategy makes it difficult to judge how best to implement guidance.
2. **No clear guidance on the role of treatment in controlling the hepatitis C epidemic.** The cost-effectiveness analyses that informed the NICE recommendations omitted the risk of patient patients with hepatitis C infecting others. However, treatment may reduce the number of infected patients and hence reduce the number of people infected. The impact of excluding infection depends on the effectiveness and costs of treatment, the prevalence of the disease and the probability of risky behaviours by infected patients.
3. **Uncertainty in the benefits of the new treatments on the health benefits to patients and costs to the NHS.** Given the small evidence base composed largely of single arm studies, there may be considerable decision uncertainty associated with recommending new treatments as cost-effective based on current information. This uncertainty imposes potentially high costs on the NHS and may imply a high value for additional research to reduce evidential uncertainty. Further analysis can inform the extent of decision

uncertainty, quantify the value of additional research and help inform implementation of NICE guidance.

4. **The potential for large upfront demand on NHS resources.** In order to release funding to offer these treatments to all eligible patients, other interventions that the NHS currently offers can no longer be funded. If the scale of demand leads to the displacement of interventions that offer more health benefits than the new treatments for chronic hepatitis C, then offering the new drugs to all eligible patients is likely to result in a net loss of health. For these reasons, implementation of NICE guidance should be informed by an analysis considering all costs and benefits to the NHS.

There is a priority for cost-effectiveness analysis which builds on NICE guidance to indicate the optimal implementation strategy for each patient group. The proposed research would include:

- A direct comparison of all the relevant treatment options, including new treatments, watchful waiting, and treatment sequences.
- Subgroup analyses by patient characteristics that affect the costs or benefits of treatment, such as genotype, prior treatment experience, interferon eligibility and severity of disease.
- The impact of uncertainty in the effects of treatment on the costs and benefits of the optimal strategies.
- The costs and benefits of reducing onward transmission and reinfection.
- The implications of current NHS England commissioning policy for treating those with decompensated cirrhosis and its impact on extending access for people with cirrhotic and non-cirrhotic disease.
- The level of investment to increase treatment uptake that is warranted alongside the optimal strategies in each of the patient groups.
- The characteristics required of any further new treatment in order for it to offer value to the NHS (threshold levels of effectiveness and cost).

2 Background and objectives

A number of new pharmaceutical therapies for chronic hepatitis C have recently been given marketing authorisation in Europe: simeprevir, sofosbuvir, ledipasvir-sofosbuvir, daclatasvir, and ombitasvir-paritaprevir-ritonavir with or without dasabuvir. These products have recently undergone or are currently undergoing appraisal of their value to the National Health Service (NHS) in England and Wales by the National Institute for Health and Care Excellence (NICE):

- Simeprevir with peginterferon alfa and ribavirin was recommended as an option for adults with genotype 1 or 4 chronic hepatitis C in February 2015 in technology appraisal (TA) 331 (1).
- Sofosbuvir with peginterferon alfa and ribavirin or with ribavirin alone was recommended as an option for adults with some genotypes and severity of chronic hepatitis C in TA330 (2).
- Ledipasvir-sofosbuvir, with or without ribavirin, is under appraisal for adults with genotype 1, 3 or 4 chronic hepatitis C (3). The appraisal consultation document is under consultation. The anticipated publication date is June 2015.
- Daclatasvir, with sofosbuvir or with pegylated interferon alfa and ribavirin is under appraisal for adults with genotype 1, 3 or 4 chronic hepatitis C (4). The anticipated publication date is August 2015.
- Ombitasvir-paritaprevir-ritonavir with or without dasabuvir is under appraisal for adults with genotype 1 or 4 chronic hepatitis C (5). The anticipated publication date is September 2015.

These new treatments are an addition to the existing interferon-based therapies. Since 2004, NICE has issued guidance on:

- Interferon alfa (pegylated and non-pegylated) and ribavirin was recommended as an option for people with chronic hepatitis C (6-9).
- Boceprevir with pegylated interferon and ribavirin was recommended as an option for adults with genotype 1 chronic hepatitis C (10).
- Telaprevir with pegylated interferon and ribavirin was recommended as an option for adults with genotype 1 chronic hepatitis C (11).

Table 1 summarises the available treatments for chronic hepatitis C: class, drug, manufacturer, licensed indication, NICE recommendations. This scoping report focusses on the drugs most recently appraised by NICE: simeprevir, sofosbuvir and ledipasvir-sofosbuvir.

Table 1 Available treatments for chronic hepatitis C (12)

Drug name	Class	Brand name - Manufacturer	Licensed indication	Appraised by NICE?
Pegylated interferon alfa	Immunomodulating drugs	Pegasys® - Roche	Indicated in combination with other medicinal products, for the treatment of chronic hepatitis C in patients with compensated liver disease.	NICE TA106 NICE TA200 NICE TA252 NICE TA300
		ViraferonPeg® – MSD	Indicated in combination with ribavirin and boceprevir, in combination with ribavirin or as monotherapy in patients with compensated liver disease.	
Interferon alfa	Immunomodulating drugs	Roferon-A® - Roche	For adult patients with histologically proven chronic hepatitis C who are positive for HCV antibodies or HCV RNA and have elevated serum alanine aminotransferase (ALT) without liver decompensation	
		IntroA® – MSD	IntronA is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for hepatitis C virus RNA (HCV-RNA).	
Ribavirin	Nucleoside analogue	Copegus® - Roche	For chronic hepatitis C (in combination with interferon alfa or peginterferon alfa)	
		Rebetol® – MSD	For chronic hepatitis C (in combination with interferon alfa or peginterferon alfa)	
Boceprevir	Protease inhibitor	Victrelis® - MSD	Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease.	NICE TA253
Telaprevir	Protease inhibitor	Incivo® – Janssen-Cilag	In combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis)	NICE TA252
Simeprevir	Protease inhibitor	Olysio® - Janssen-Cilag	In combination with other medicinal products for the treatment of chronic hepatitis C in adult patients. The posology is specified for people with genotypes 1 or 4 chronic hepatitis C.	NICE TA331
Sofosbuvir	Inhibitor of the NS5B polymerase	Sovaldi ® - Gilead	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. The posology is specified for people with genotypes 1, 2, 3, 4, 5 and 6 chronic hepatitis C.	NICE TA332
Ledipasvir-sofosbuvir	Inhibitor of the NS5A polymerase	Harvoni ® - Gilead	Indicated for the treatment of chronic hepatitis C in adults. The posology is specified for people with genotypes 1, 3 or 4 chronic hepatitis C.	Under appraisal
Daclatasvir	Inhibitor of the NS5A polymerase	Daclinza ® - Bristol-Myers Squibb	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus. The posology is specified for genotypes 1, 3 and 4.	Under appraisal
Ombitasvir-paritaprevir-ritonavir with or without dasabuvir	Inhibitor of the NS5A, NS5B and NS3/4A	Viekirax ® - AbbVie	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. The posology is indicated for genotypes 1a, 1b and 4.	Under appraisal

NICE has endeavoured to produce timely guidance on the effectiveness and cost-effectiveness of the new treatments, particularly given the disease burden of chronic hepatitis C and the high acquisition cost of the new treatments. Therefore, the new treatments have been appraised using the single technology appraisal (STA) process so that guidance and evidence summaries could be produced close to regulatory approval. Since the new drugs have been licensed almost concurrently, the STA process does not incorporate a direct comparison between all of them[1]. A consequence of the STA process is that multiple drugs may be recommended as 'an option' without a clear position on their respective roles in the treatment pathway. As a result, the NHS and commissioners face the challenge of how best to implement NICE guidance given the multiple recommendations as 'an option', the large population eligible for treatment, and high acquisition costs.

In allocating resources to treatments for hepatitis C, therefore, the NHS has to address a number of questions regarding the implementation of NICE guidance:

- What is the magnitude of the cost-effectiveness of new therapies for hepatitis C and how does this vary between subgroups?
- What are the implications for population health given the size of the patient groups and the high acquisition cost of these therapies?
- Given information on the magnitude of cost-effectiveness and size of the patient groups, how should the NHS manage implementation of NICE guidance?

Various types of economic analysis can be undertaken to inform these and other questions. These analyses have varying time and other resource implications. Some types of research may also amount to re-doing analyses which have been undertaken as part of NICE STAs or which could be undertaken by NICE in the future, which is duplicative and potentially inefficient. Therefore, a careful assessment is required of which types of research EEPRU might undertake over a range of possible timelines.

[1] The STA process often begins before the license is obtained. Hence other treatments entering the process at the same time are outside the NICE scope. In addition, a large proportion of the evidence is outside the public domain and is known only to the company that holds the patent for each product. Therefore, the possibility to make any direct comparisons is limited.

2.1 Objectives

The aim of this work is to provide a basis for decisions about substantive research which could be undertaken to inform NHS decisions about the implementation of NICE guidance on hepatitis C drugs. The specific objectives are:

- To summarise the key information and recommendations from the most recent published NICE STAs (simeprevir, sofosbuvir and ledipasvir-sofosbuvir).
- To provide estimates of the treatment cost implied by existing NICE guidance.
- To identify the gaps in the existing evidence base and the issues raised for the NHS by NICE guidance.
- To suggest areas where further analysis is required to inform NHS policy on implementation of NICE guidance.

3 Methods

The publicly available documentation on the NICE TAs provides information on the NICE recommendations, health benefits, acquisition costs and cost-effectiveness (i.e. value to the NHS) of simeprevir, sofosbuvir and ledipasvir-sofosbuvir. Their health benefits are expressed in terms of quality-adjusted life years (QALYs) gained compared with the older treatments. QALYs measure the length of life adjusted for the health-related quality of life experienced. Their clinical effectiveness is expressed as the proportion of patients achieving sustained virologic response (SVR), which is widely accepted to equate to cure. The acquisition costs refer to the costs of purchasing the drug using the price quoted in the NICE TA over the recommended treatment duration. The cost-effectiveness, or value to the NHS, is represented by the incremental cost-effectiveness ratio (ICER) compared with the next best alternative. NICE assesses whether a new intervention is good value for the NHS by comparing the ICER to a cost-effectiveness threshold. This is equivalent to comparing the health benefits achieved by the new intervention with its opportunity cost, where the latter is the health forgone elsewhere in the NHS from diverting resources to fund the new intervention. The impact of treatment for chronic hepatitis C on onward transmission was obtained from previously published academic studies (13-17). The size of the patient population and subgroups was obtained from Public Health England and the manufacturer's submission of sofosbuvir to NICE (18, 19). The treatment cost of NICE guidance was estimated for a range of scenarios. Further detail on the methods is presented in the Technical Appendix.

4 Results

4.1 NICE recommendations

Table 2 and Figure 1 summarise the recommendations in subpopulations defined by genotype, disease severity (cirrhotic or non-cirrhotic) and treatment status (treatment naïve, treatment experienced and eligibility for treatment with interferon-based treatments). The Technical Appendix summarises the effectiveness and cost-effectiveness information underpinning the NICE recommendations (see Section 9.4) .

Given the previous NICE recommendations, pegylated interferon with ribavirin is an option for all patients with chronic hepatitis C regardless of genotype (6-9). Boceprevir or telaprevir in combination with pegylated interferon and ribavirin are options for people with genotype 1 chronic hepatitis C (10, 11). The new treatments offer additional treatment possibilities:

- Simeprevir and sofosbuvir, in combination with pegylated interferon and ribavirin, and ledipasvir-sofosbuvir have been recommended by NICE as options for people with genotype 1 chronic hepatitis C, except for people who are treatment experienced with cirrhosis (1-3).
- Sofosbuvir with ribavirin was recommended by NICE in treatment experienced or interferon ineligible people with genotype 2 chronic hepatitis C (2).
- Sofosbuvir with pegylated interferon and ribavirin was recommended by NICE as an option for people with genotype 3 who are non-cirrhotic and treatment-experienced or cirrhotic regardless of prior treatment;
- Sofosbuvir and ribavirin was recommended by NICE for people with genotype 3 cirrhotic who cannot have interferon (2).
- Simeprevir with pegylated interferon and ribavirin was recommended by NICE for all patients with genotype 4
- Sofosbuvir with pegylated interferon and ribavirin was recommended by NICE for genotype 4 cirrhotic patients
- Ledipasvir-sofosbuvir was recommended by NICE for genotype 4 non-cirrhotic treatment experienced or cirrhotic treatment naïve (1-3).
- Sofosbuvir with pegylated interferon and ribavirin was recommended by NICE as an option for cirrhotic people with genotype 5 or 6 chronic hepatitis C (2).

Table 2 NICE recommendations by subgroup (1-3)

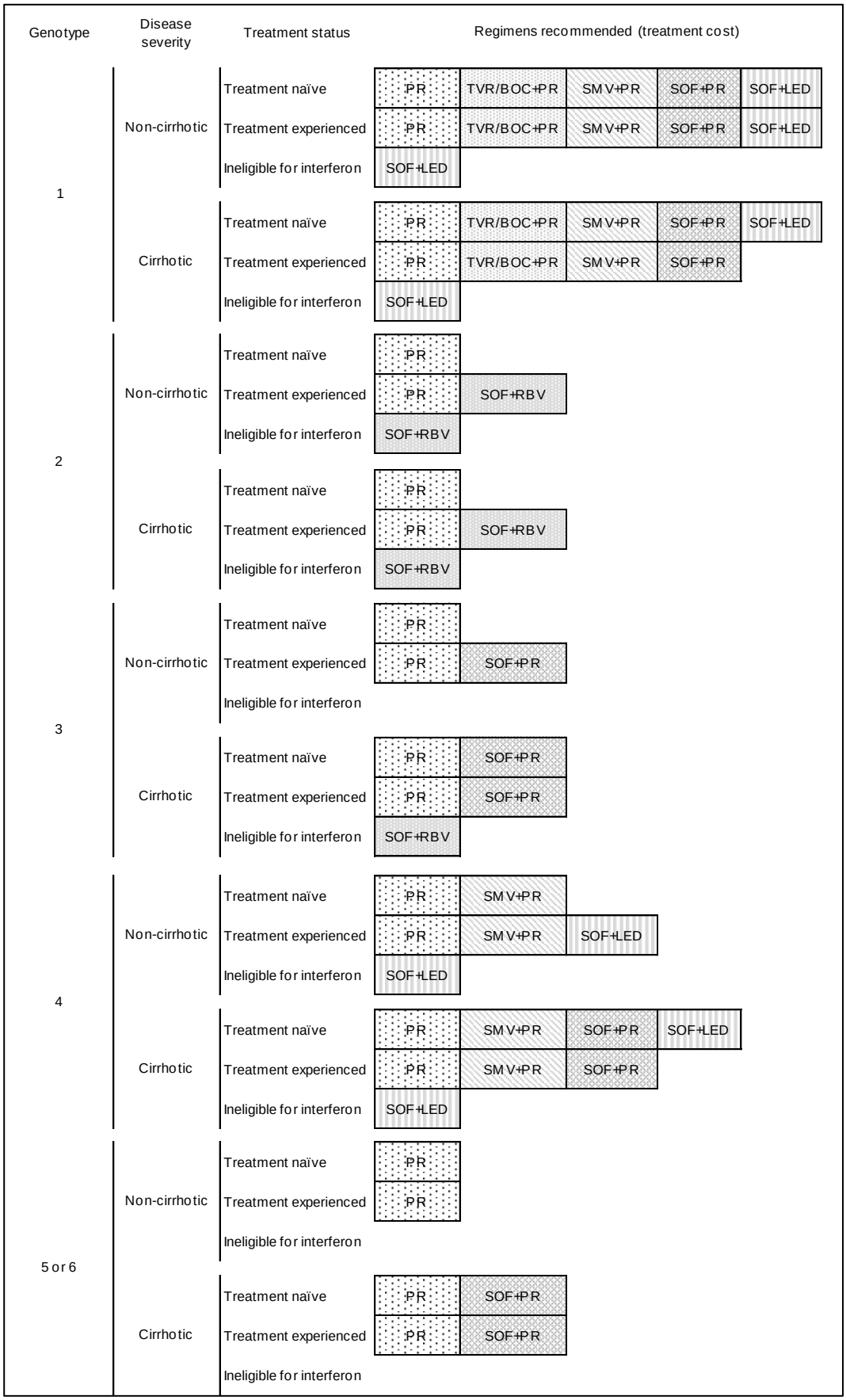
Genotype	Disease severity	Treatment status	Treatments recommended			
			SMV+PR	SOF+PR	SOF+RBV	SOF+LED
1	Non-cirrhotic	Treatment naïve	12+24 weeks	12 weeks	NR	8 weeks
		Treatment experienced	12+48 weeks [a]	12 weeks	NR	12 weeks
		Ineligible for interferon	Not applicable	Not applicable	NR	Subgroup not considered
	Cirrhotic	Treatment naïve	12+24 weeks	12 weeks	NR	12 weeks
		Treatment experienced	12+24 weeks [a]	12 weeks	NR	NR
		Ineligible for interferon	Not applicable	Not applicable	NR	Subgroup not considered
2	Non-cirrhotic	Treatment naïve	Not licensed in genotype 2	Not licensed in genotype 2	NR	Not licensed in 2
		Treatment experienced			12 weeks	
		Ineligible for interferon			12 weeks	
	Cirrhotic	Treatment naïve			NR	
		Treatment experienced			12 weeks	
		Ineligible for interferon			12 weeks	
3	Non-cirrhotic	Treatment naïve	Not licensed in genotype 3	NR	NR	Not licensed in genotype 3[c]
		Treatment experienced		12 weeks	NR	
		Ineligible for interferon		Not applicable	NR	
	Cirrhotic	Treatment naïve		12 weeks	NR	
		Treatment experienced		12 weeks	NR	
		Ineligible for interferon		Not applicable	24 weeks	
4	Non-cirrhotic	Treatment naïve	12+24 weeks	NR	NR	NR
		Treatment experienced	12+48 weeks [a]	NR	NR	12 weeks
		Ineligible for interferon	Not applicable	Not applicable	NR	Subgroup not considered
	Cirrhotic	Treatment naïve	12+24 weeks	12 weeks	NR	12 weeks
		Treatment experienced	12+48 weeks [a]	12 weeks	NR	NR
		Ineligible for interferon	Not applicable	Not applicable	NR	Subgroup not considered
5 or 6	Non-cirrhotic	Treatment naïve	Not licensed in genotype 5 and 6.	NR	NR	Not licensed in genotype 5 and 6.
		Treatment experienced		NR	NR	
		Ineligible for interferon		Not applicable	NR	
	Cirrhotic	Treatment naïve		12 weeks	NR	
		Treatment experienced		12 weeks	NR	
		Ineligible for interferon		Not applicable	NR	

SOF+PR: sofosbuvir + pegylated interferon alfa and ribavirin; SOF+RBV: sofosbuvir + ribavirin; SOF+LED: sofosbuvir + ledipasvir; SMV+PR: simeprevir + pegylated interferon alfa and ribavirin.; NR – not recommended.

(a) SMV is not recommended in patients who have previously failed with other protease-inhibitors.

(b) LED+SOF+RBV licensed for genotype 3 but not recommended by NICE.

Figure 1 NICE recommendations by subgroup (1-3)



PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

The costs of the new treatments are (in ascending order; all exclude value added tax (VAT)):

- £25,987 for a 8-week course of ledipasvir-sofosbuvir (this was calculated using the cost per 28 tablet pack at £12,993.33 reported in the NICE appraisal consultation document for ledipasvir-sofosbuvir (3));
- £27,220 for a 12-week course of simeprevir with 24 weeks of pegylated interferon (reported in the NICE final appraisal determination for simeprevir (1));
- £32,155 for a 12-week course of simeprevir with 48 weeks of pegylated interferon (reported in the NICE final appraisal determination for simeprevir (1));
- £37,585 for 12 weeks of sofosbuvir with pegylated interferon and ribavirin (calculated using the cost of sofosbuvir at £2,915.22 per week, the cost of pegylated interferon at £124.40 per week and the cost of ribavirin at £92.49 per week, based on Table 58 of the manufacturer's submission on sofosbuvir (19)). However, in subgroups with risk factors associated with poor response, the cost per treatment-course can increase up to £75,171 (24 weeks of treatment, calculated using the assumptions above; more details on the patients' characteristics associated with an increase in treatment costs are below).
- £38,980 for 12 weeks of ledipasvir-sofosbuvir (this was calculated using the cost per 28 tablet pack at £12,993.33 reported in the NICE appraisal consultation document for ledipasvir-sofosbuvir (3));
- and £72,951 for 24 weeks of sofosbuvir with ribavirin(1-3, 19) calculated using the cost of sofosbuvir at £2,915.22 per week and the cost of ribavirin at £92.49 per week, based on Table 58 of the manufacturer's submission on sofosbuvir (19)).

The treatment costs in clinical practice may vary depending of the patients' characteristics. The costs of sofosbuvir with pegylated interferon and ribavirin may increase, since the license specifies that consideration should be given to extending the duration of therapy beyond 12 weeks and up to 24 weeks. This is especially for those subgroups which have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non-CC genotype, prior null response to peginterferon alfa and ribavirin therapy) (20). The costs of simeprevir with pegylated interferon and ribavirin are lower in patients who meet the treatment stopping rules (21).

For the treatment ledipasvir-sofosbuvir, the NICE committee specified the recommended treatment durations based on its product license (3, 22). For genotype 1 chronic hepatitis C, 8 weeks is the only NICE recommended duration for treatment-naïve patients without cirrhosis. Twelve weeks is the only NICE-recommended duration for cirrhotic patients who are either treatment-naïve or treatment-experienced. In people with genotype 4 chronic hepatitis C, 12 weeks of treatment was

recommended for patients who are treatment-naïve with cirrhosis or treatment-experienced without cirrhosis.

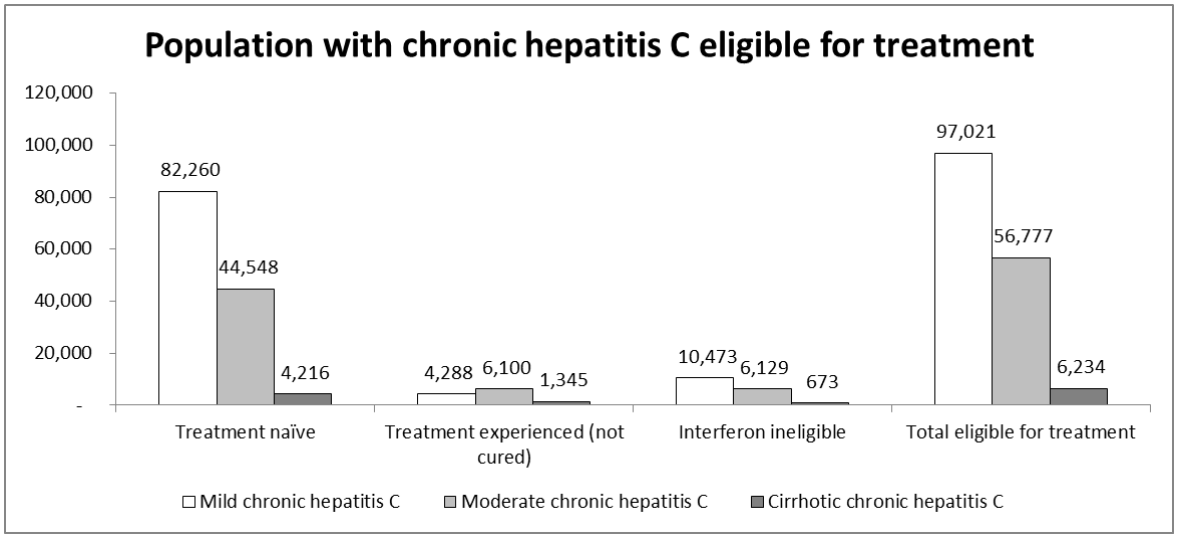
The acquisition costs of the new treatments are much greater than the current existing therapies. The duration of dual therapy with pegylated interferon alfa and ribavirin varies according to genotype and response to treatment at week 4 and 24 (rapid viral response; RVR) (23). Treatment duration varies depending on patients' characteristics and response to treatment. Using the unit costs of the manufacturer's submission on sofosbuvir (Table 58)(19), the cost of a course of pegylated interferon alfa and ribavirin is £3,470 for 16 weeks, £5,205 for 24 weeks and £10,411 for 48 weeks (this assumes a cost of pegylated interferon at £124.40 and a cost of ribavirin at £92.49 per week (19)). This is ten to four times less than the cost of the new treatments.

The other protease inhibitors recommended by NICE, boceprevir and telaprevir, are used in combination with pegylated interferon alfa and ribavirin. The treatment course of boceprevir varies between £22,873 and £32,811 depending on patients' characteristics and response to treatment (this uses the cost of pegylated interferon at £124.40 and a cost of ribavirin at £92.49 per week from Table 58 of the manufacturer's submission on sofosbuvir and the boceprevir at £700 per week (11)). The treatment course of telaprevir costs between £27,603 and £32,809 (same unit costs for pegylated interferon and ribavirin and the cost of telaprevir at £1,866.50 per week (10, 19)). The future availability of boceprevir and telaprevir in the UK is unclear given the recent market withdrawals of both drugs from the US (24).

4.2 The size of the patient population

Figure 2 presents the estimated number of people infected with chronic hepatitis C at stages prior to decompensated cirrhosis (25). These represent all patients with chronic hepatitis C, including those not diagnosed. The estimates were obtained from a population model of the chronic hepatitis C, using information on the number of people with end-stage liver disease, hepatocellular cancer and death from liver disease from Hospital Episode Statistics (HES) and Office of National Statistics (ONS) up to 2009 (25). The model estimates approximately 160,000 people with chronic hepatitis C: 97,021 with mild disease, 56,777 with moderate disease and 6,234 with cirrhotic disease. Of these, 5%, 12% and 24% respectively have been previously treated without successful eradication of the infection (treatment experienced). In addition, 11% of people are assumed to be ineligible for interferon-based treatment (19). Harris et al estimated that 5,000 patients (approximately 3% of people with chronic hepatitis C) were treated in 2011 based on number of doses of pegylated interferon purchased or supplied in England (25).

Figure 2 People with chronic hepatitis C in England (25)



The genotypes of the chronic hepatitis C virus that are most prevalent in England are genotype 1 (45%) and 3 (44%); 7% are genotype 2 and the remaining 4% are genotypes 4, 5 or 6 (18, 19). The distribution of patients by disease severity was assumed to be the same across genotypes.

4.3 Treatment cost scenarios

The treatment cost over one year of the treatments for chronic hepatitis C was calculated for four scenarios assuming (i) the current treatment uptake of 3% (25) and (ii) treatment uptake of 100%. The technical appendix provides details on the calculations and shows the full results.

- **Scenario 1, boceprevir or telaprevir**: Boceprevir or telaprevir (whichever is less costly) in combination with pegylated interferon and ribavirin for genotype 1 patients eligible for interferon-based therapy as per NICE recommendations; pegylated interferon and ribavirin for all other patients eligible for interferon-based therapy; patients ineligible for interferon do not receive treatment.
- **Scenario 2, simeprevir**: Simeprevir in combination with pegylated interferon and ribavirin for genotype 1 and 4 patients eligible for interferon-based therapy as per NICE recommendations; pegylated interferon and ribavirin for all other patients eligible for interferon-based therapy; patients ineligible for interferon do not receive treatment.
- **Scenario 3, sofosbuvir**: Sofosbuvir in combination with pegylated interferon and ribavirin or only in combination with ribavirin for the genotypes and disease severity as per NICE recommendations; pegylated interferon and ribavirin for all other patients eligible for

interferon-based therapy; patients ineligible for interferon who are not covered by the NICE recommendations do not receive treatment.

- **Scenario 4, ledipasvir-sofosbuvir**: ledipasvir-sofosbuvir for patients with genotype 1 or 4 as per NICE recommendations; all other patients eligible for interferon-based therapy receive pegylated interferon and ribavirin; patients ineligible for interferon who are not covered by the NICE recommendations do not receive treatment.

Figure 3 shows the treatment cost over one year assuming 3% treatment uptake (25); Figure 4 shows the same estimates but assumes an uptake of 100%. Scenario 1 aims to mimic the situation before the emergence of the new treatments. People with genotype 1 chronic hepatitis C are treated with boceprevir or telaprevir in combination with pegylated interferon and ribavirin unless they are ineligible for interferon. This represents a cost of £52 million assuming 3% uptake and £1,734 million pounds assuming 100% people eligible for interferon therapy with genotype 1 are treated. The people with genotypes other than genotype 1 eligible for interferon treatment are treated with pegylated interferon with ribavirin at a cost of £10 million assuming 3% uptake or £331 million assuming 100% uptake. People not eligible for interferon based therapy do not receive treatment (N=17,275). The total cost is £62 million assuming 3% uptake and £2,065 million assuming 100% uptake.

Scenario 2 shows the treatment cost assuming that eligible patients receive simeprevir with pegylated interferon and ribavirin. Therefore, people with genotype 1 eligible for interferon based therapy and people with genotype 4 eligible for interferon based therapy receive simeprevir treatment. The cost of simeprevir with pegylated interferon and ribavirin over one year is £58 million assuming 3% uptake and £1,943 million assuming 100%. People with genotype 2 or 3 eligible for interferon therapy are treated with pegylated interferon and ribavirin at a cost of £9 million assuming 3% uptake or £285 million assuming 100%. People not eligible for interferon based therapy do not receive treatment (N=17,275). The total cost is £67 million, an increase of £5 million over scenario 1 assuming 3% uptake, and £2,228, an increase of £163 million over scenario 1 assuming 100% uptake.

Scenario 3 shows the treatment cost assuming that eligible patients receive sofosbuvir with pegylated interferon and ribavirin, or sofosbuvir with ribavirin as per NICE recommendations. The budget impact of treating eligible people with sofosbuvir with pegylated interferon and ribavirin is £79 million assuming 3% uptake and £2,649 million assuming 100%. The cost of treating eligible people with sofosbuvir with ribavirin is £3 million assuming 3% uptake and £98 million assuming 100%. The cost of treating the remaining people eligible for interferon-based therapy is £9 million assuming 3% uptake and £298 million assuming 100%. People not eligible for interferon-based

therapy who are not recommended sofosbuvir with ribavirin do not receive treatment (N=15,720). The total cost is £91 million, an increase of £29 million over scenario 1 assuming 3% uptake, and £3,044 million, an increase of £980 million over scenario 1 assuming 100% uptake.

Scenario 4 shows the treatment cost assuming that all eligible patients receive ledipasvir-sofosbuvir as per NICE recommendations. Patients who are not eligible for this treatment receive pegylated interferon with ribavirin. The cost of ledipasvir-sofosbuvir is £60 million assuming 3% uptake and £1,994 assuming 100%. The cost of pegylated interferon with ribavirin is £10 million assuming 3% uptake and £331 million assuming 100%. People not eligible for interferon based therapy do not receive treatment (N=8,828). The total cost is £70 million, an increase of £8 million over scenario 1 assuming 3% uptake, and £2,324, an increase of £259 million over scenario 1 assuming 100% uptake.

Figure 3 Treatment cost over one year assuming 3% (25) treatment uptake

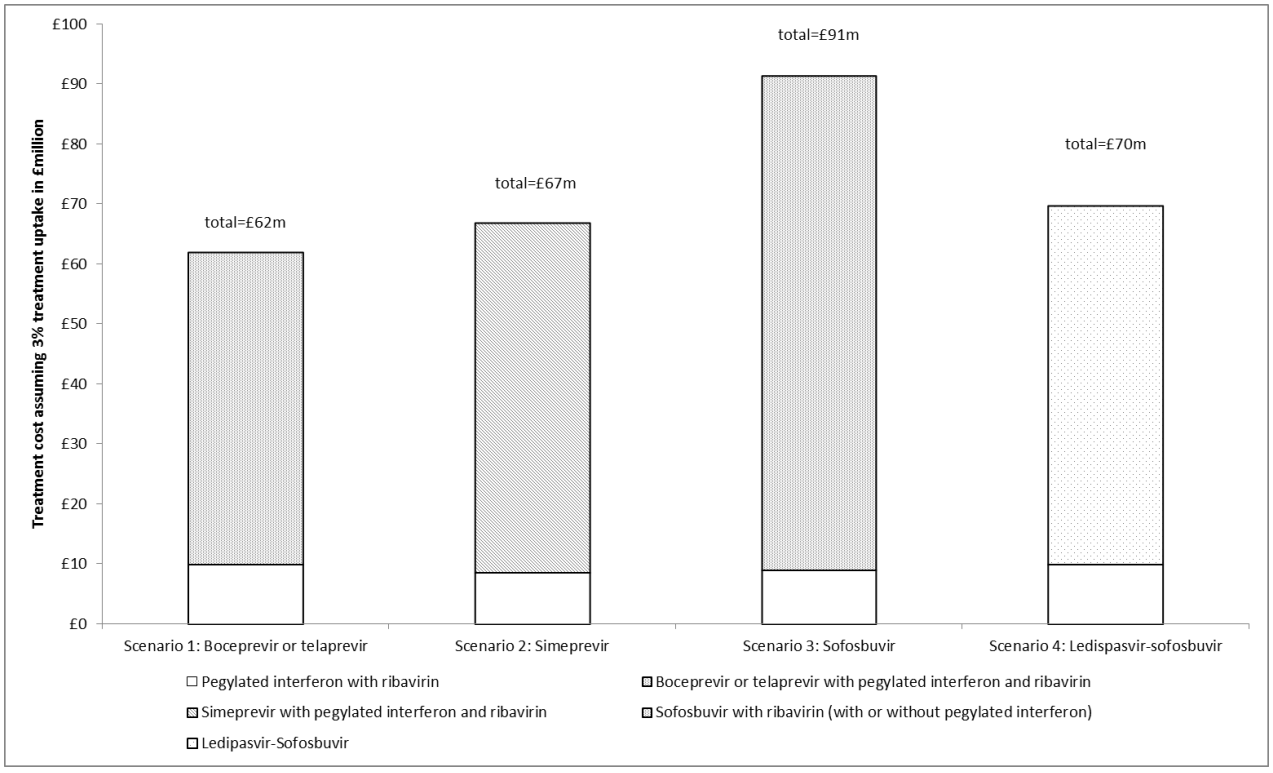
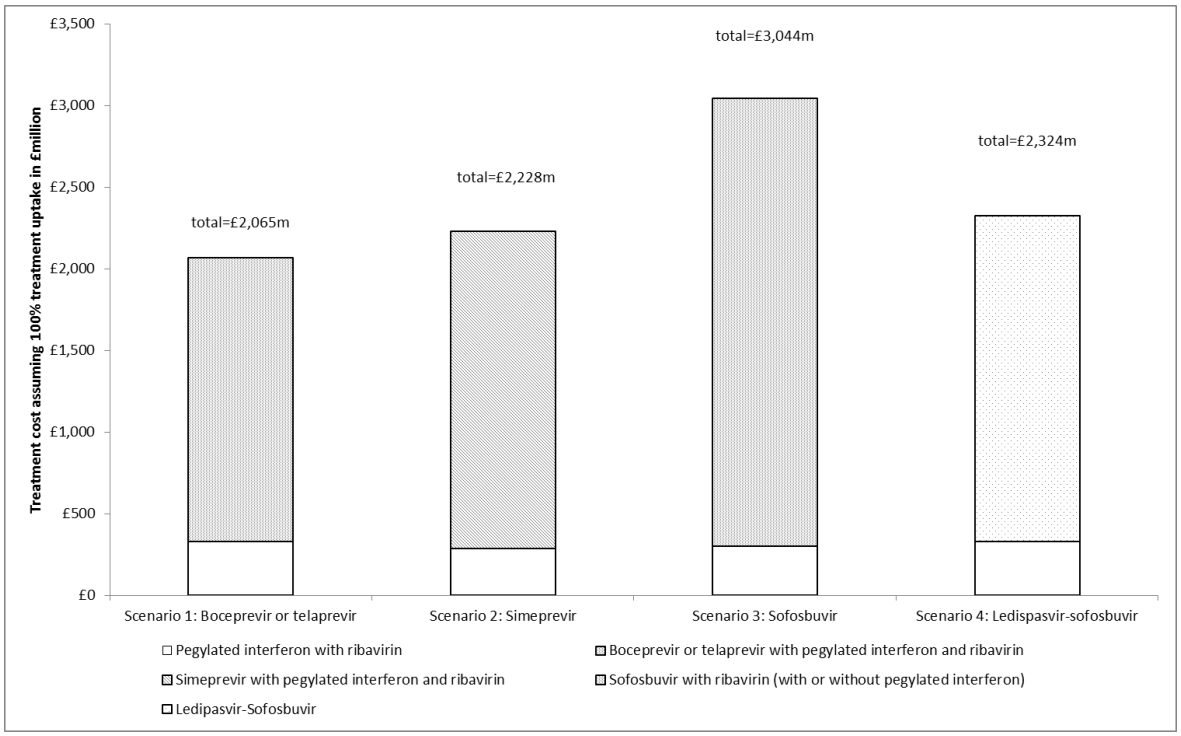


Figure 4 Treatment cost over 1 year assuming 100% treatment uptake



4.4 Prioritisation scenarios

The NICE STAs have considered whether, for a given patient at a particular stage in their disease and treatment for hepatitis C, one of the new drugs might provide value. However, the results do not lend themselves to directly inform strategies about prioritising access to new drugs for hepatitis C in a way that maximises health benefits and value to the NHS.

Watchful waiting consists of monitoring the patient until their disease progresses to a more severe stage and then treating. Watchful waiting may represent current practice. Watchful waiting strategies were considered implicitly in the NICE STAs in that some treatments were recommended for more severe patients (i.e. patients with cirrhosis) but not for patients with less severe disease (i.e. patients without cirrhosis). For example, NICE recommended sofosbuvir with pegylated interferon and ribavirin for people with genotype 4 chronic hepatitis C with cirrhosis but not for people without cirrhosis. Watchful waiting strategies may be particularly cost-effective for patients with mild disease and a low likelihood of onward transmission. For example, in a prospective study following 2,235 people with chronic hepatitis C, the median time for progression to cirrhosis was 30 years (increasing to 42 years among women who do not consume alcohol (26) On average, only 10%-20% of people with chronic hepatitis C will develop cirrhosis over a 20 year period (3, 26). If the aim of treatment is to reduce the incidence of events with a high health burden or health care costs (decompensated cirrhosis, end stage liver disease, liver transplant), then making new drugs available

to all patients with chronic hepatitis C could represent overtreatment as up to 80% of those receiving high cost drugs would, in the absence of those drugs, have experienced little or no ill health consequences from their disease over the next 20 years. The question about at what stage of disease progression (e.g. METAVIR stage, cirrhosis) is it most valuable for the NHS to target treatment has not been be fully addressed by existing analyses and requires further cost effectiveness research.

A related prioritisation strategy is that of *treatment sequencing*. This involves initially treating people with a less costly and less effective treatment (e.g. pegylated interferon with ribavirin), then retreating people who do not achieve SVR (treatment failures) with more expensive and more effective treatment (e.g. ledipasvir-sofosbuvir or others).[2] By classifying patients into treatment-naïve and treatment-experienced, the existing NICE guidance implicitly sets out a treatment sequence. For example, in non-cirrhotic people with genotype 4 chronic hepatitis C, ledipasvir-sofosbuvir is recommended for treatment-experienced but not for treatment-naïve. In practice, this is a treatment sequencing strategy by which only people who failed in other treatments are recommended treatment with ledipasvir-sofosbuvir. As many patients will respond to the older drugs, a treatment sequencing approach can enable a very high rate of cure to be achieved without requiring that all patients to receive the new drug. For example, if current therapy achieves SVR in 40% of patients at a cost of £9,000 while a new drug achieves SVR in 100% of patients at a cost of £30,000, then treating only those that fail current therapy with the new drug achieves 100% cure rate at a cost of £27,000 per patient (1*9000+[1-0.4]*30000): a saving of £3,000 per patient compared with giving all patients the new drug. The question about which treatment sequences are feasible and of value to the NHS has not been addressed in existing analyses and requires further work.

4.5 The impact of infection on costs and health benefits

The cost-effectiveness analyses that informed the NICE recommendations omitted the risk of patient patients with hepatitis C infecting others (i.e. they were static models not allowing for the dynamic effect of the disease). In other words, these analyses assumed that the number of infected patients (prevalence) has no impact on the number of new infections (incidence). In reality, treatment may reduce the number of infected patients and hence reduce the number of new infections. This has implications for the costs and health benefits from these new treatments. Infections may occur in previously treated patients (reinfection) or in patients who have never had the disease (new

[2] This might be considered jointly with a watchful waiting approach in terms of what treatment might be suitable for patients before they require access to new drugs.

infections). Excluding reinfection is likely to overestimate the benefits and underestimate the costs of more effective treatments since re-infected patients require new treatment. Conversely, excluding new infections may underestimate the benefits of more effective treatments. The impact of excluding reinfection and new infections depends on the effectiveness and costs of treatment, the prevalence of the disease and the probability of risky behaviours by infected patients.

There is some research on the impact of reinfection and new infections on the costs and health benefits of the new treatments (13-16). Martin *et al* developed a model with two components: a dynamic model to simulate the new infections among current injecting drug users (people who inject drugs (PWID)), and a static component to simulate the natural history of chronic hepatitis C in current or ex-PWID (17). The model compared the costs and benefits of a strategy to treat a PWID at the mild stage, a PWID at the moderate stage, a non- or ex injector at the mild stage or a non- or ex-infector at the moderate stage in a population of 1,000 PWID, in addition to treating all patients with compensated cirrhosis. This work suggests that the treating moderate PWIDs is cost-effective in settings with prevalence of chronic hepatitis C among PWID of between 20-40%. However, when prevalence is 60%, the cost-effective strategy is to prioritise non- or ex-injectors since the benefits of reduced onward transmission are outweighed by the costs of reinfection. Earlier work by the same team suggests that the costs and benefits of treatment are very sensitive to treatment uptake by PWID (16).

Although this model addresses one of the key issues raised by the NICE guidance, it has a number of limitations to inform the commissioning decisions by NHS England. The model evaluates the costs and benefits of a hypothetical direct-acting anti-viral treatment for chronic hepatitis C; it does not include differences in treatment duration (and hence in costs) by patient group; it does not include watchful waiting or treatment sequencing strategies and it does not allow for retreatment after treatment failure.

5 Gaps in the evidence base

The ongoing development of NICE guidance raises a number of issues that can affect its implementation by NHS England. Although the level of funding required is difficult to predict, there is a legal requirement that funding for all positive advice arising from TAs should be made available with three months of publication (27). As discussed in Section 4.4 on treatment cost, the funding required to make the new treatments available varies from £62 million to £3,044 million depending on the scenarios considered. The plausibility of each scenario depends on how NICE guidance is interpreted and prioritised for implementation and on whether additional investment is made to

improve treatment uptake. The issues raised by the NICE guidance in the operationalization of its implementation by NHS England are discussed below.

5.1 The challenges posed by NICE STA in chronic hepatitis C

The first issue is related to the NICE STA process in the context of rapidly evolving current practice and the quick emergence of new therapies. The NICE STA process offers an efficient and timely appraisal process of new technologies close to regulatory approval and launch. The new technology is compared with its relevant comparators, which are defined in the NICE scope. A comparator technology is one that is currently used in the NHS and could be replaced by the intervention, if recommended (28). However, current practice in the treatment of chronic hepatitis C is evolving as new therapies emerge and older therapies are discontinued. As a result, the new technologies that were licensed and appraised earlier are not compared directly against those new technologies licensed and appraised later. In technologies appraised concurrently, such as simeprevir and sofosbuvir, each treatment is compared against current practice but not with against each other. In addition, NICE cannot issue guidance on a comparator under the STA process. In a situation where a treatment that had been approved earlier as 'an option' but was found not to be cost-effective when subsequently compared with a new technology, the existing guidance recommending this comparator as an option remains valid. Therefore, a number of treatments are recommended options for chronic hepatitis C. For example, the recommended options for genotype 1 chronic hepatitis C are the new treatments simeprevir or sofosbuvir in combination with pegylated interferon alfa and ribavirin, older protease inhibitors telaprevir or boceprevir in combination with pegylated interferon alfa and ribavirin, ledipasvir-sofosbuvir, and dual therapy with pegylated interferon alfa and ribavirin (see Figure 1). Consequently, it may be difficult for the NHS to define which patient groups and which treatments should be prioritised for implementation of NICE guidance.

An additional challenge posed by the NICE STA guidance on the new treatments for chronic hepatitis C is the lack of the explicit incorporation of watchful waiting and treatment sequencing strategies. The NICE guidance implicitly recommends watchful waiting and treatment sequencing strategies as options (see discussion in Section 4.4). However, the different types of strategies (watchful waiting, treatment sequencing and treat all) were not compared directly. Therefore, the magnitude of cost-effectiveness, which in turn has implications for the level of investment that is appropriate for the NHS to make to implement a cost-effectiveness strategy, is unclear. As a result, it is difficult to manage the implementation of the new treatments.

5.2 The impact of benefits from reduced onward transmission

Treatment for chronic hepatitis C may have additional health benefits and cost savings resulting from the reduction in the prevalence in the disease and hence in the risk of onward transmission. These benefits are likely to differ depending on the effectiveness and uptake of the different treatments, the prevalence of the disease and the probability of risky behaviours in different patient groups (13-17). However, the cost-effectiveness models informing the NICE guidance failed to appropriately characterise the possibility of reinfection or onward transmission, with the majority excluding them altogether. Excluding reinfection is likely to overestimate the benefits and underestimate the costs of more effective treatments since re-infected patients may experience further health losses from the disease and require new treatment. Excluding onward transmission may underestimate the benefits of more effective treatments. For these reasons, it is unclear how the inclusion of the possibility of reinfection and onward transmission may affect the cost-effectiveness of the different treatment strategies. The costs and health consequences of reinfection and onward transmission should be considered in the cost-effectiveness analysis of the different treatment strategies.

5.3 The impact of uncertainty on costs and health benefits

A third issue is the impact of uncertainty in the benefits of the new treatments on the health benefits to patients and costs to the NHS. Research has shown that the uncertainty relating to the costs and effects of new technologies can lead to health losses and additional costs to the NHS (29, 30). In other words, there may be considerable *decision uncertainty* associated with recommending treatments that are expected to be cost-effective under the current evidence when that evidence is itself uncertain. This decision uncertainty imposes costs (which can be expressed in terms of resource costs or population health) on the NHS.

In the context of chronic hepatitis C, the evidence base for the new treatments is small, particularly in patients with cirrhosis, in less prevalence genotypes and in harder to reach populations, such as those who inject drugs. As a result, the evidence on the effectiveness of treatment is uncertain. The implication is that there may be considerable decision uncertainty associated with recommending new treatments as cost-effective based on the current information from clinical studies. This uncertainty imposes potentially high costs on the NHS and which implies a high value for additional research to reduce evidential uncertainty. Further analysis can inform the extent of decision uncertainty and quantify the value of additional research. Further evidence may be forthcoming

through, for example, the early access scheme run by NHS England on the effectiveness of the new treatment treatments for people with decompensated cirrhosis. In addition, further analysis may suggest a need for additional randomised trials or other forms of research. There is also uncertainty about how to prioritise between treatment strategies if constraints in key resources (e.g. health care professionals, diagnostic and monitoring equipment) preclude offering all the recommended options to all eligible patients, or if the NHS is unable to disinvest in other activities sufficiently rapidly to free-up resources to fund the new hepatitis C products. This issue relates to the discussion under point 1 above. STAs were not designed to help inform guidance on multiple strategies, but to assess whether a specific intervention is a cost-effective option. As a result, there is uncertainty on how to manage the implementation of NICE guidance and how to prioritise the new treatments.

5.4 The opportunity costs of high cost medications affecting large populations

The cost-effectiveness threshold used NICE is £20,000 to £30,000 per QALY gained (31). The NICE cost-effectiveness threshold represents the opportunity costs of devoting resources to the new technology, in terms of health benefits forgone as a result of those resources being unavailable to fund other alternative competing priorities (32). In addition to forgone health, the NICE Committee may also consider other factors, such as innovation and unmet need (31). In summary, a new technology is considered to be cost-effective on a per patient basis if the incremental cost-effectiveness ratio (ICER) is below a threshold between £20,000 and £30,000 per QALY.

Recent empirical research on the cost-effectiveness threshold to inform NICE decisions has estimated that the additional cost which results in 1 QALY being forgone by NHS patients is approximately £13,000 (32), lower than implied by the existing NICE threshold range. Furthermore, this research highlighted that technologies with non-marginal cost impact on the NHS budget are likely to displace disproportionally more health, implying an even lower cost-effectiveness threshold. The new treatments for chronic hepatitis C represent a non-marginal budget impact given their high acquisition cost and large patient population.

The scenarios on treatment costs suggest that higher treatment uptake than is currently the case involve the NHS incurring large upfront costs. Assuming that all eligible patients come forward for treatment, the acquisition costs of treatment are £2,952 million (Scenario 2: Simeprevir), £4,034 million (Scenario 3: Sofosbuvir) or £3,079 million (Scenario 4: Ledipasvir-sofosbuvir). Overall, NHS England has a budget of £95.6 billion for 2013/14 (33), with approximately 10% is allocated to prescription medicines (34). Each of these scenarios corresponds to 31% to 42% of the total NHS budget for medicines. In order to release funding to offer these treatments to all eligible patients,

other interventions that the NHS currently offers can no longer be funded. These interventions may offer more health benefits to the patients receiving them than the new treatments for chronic hepatitis C offer. Therefore, offering these new drugs to all eligible patients is likely to result in a net loss of health. For these reasons, implementation of NICE guidance should be informed by an analysis considering all costs and benefits to the NHS.

6 What research is needed now?

In implementing NICE guidance, the NHS should seek the optimal treatment strategy for each patient group. That is, the treatment strategy that achieves the greatest net impact on population health. Similarly, to increase implementation of new treatments for hepatitis C, the investment should also be determined by the magnitude of the gains in population (i.e. by how cost-effective the new intervention is). Highly cost-effective strategies may warrant greater investment in implementation. However, and for the reasons discussed above, the NICE STA guidance does not provide all the information required to choose which interventions to implement first and for whom. In addition, implementation of NICE guidance may result in a net loss of health given the large treatment cost. Hence, there is a need for research that can inform NHS commissioning decisions by addressing the issues in the NICE guidance and the gaps in the evidence.

There is a priority for cost-effectiveness analysis which builds on NICE guidance, and is undertaken in collaboration with NHS England, Public Health England and the University of Bristol, to indicate the optimal treatment strategy for each patient group. The technical appendix details the proposed research. In brief, it involves the development of a new decision model using the same inputs as the NICE appraisals to ensure that the evaluation is consistent with NICE guidance and reduces the time and resources required to develop the model.

The proposed research would include:

- All the relevant treatment options, including all new treatments, watchful waiting for people with milder disease and low probability of transmission, and treatment sequences.
- The costs and benefits of reducing onward transmission and reinfection.
- The implications for people with cirrhotic and non-cirrhotic disease from treating people with decompensated cirrhosis as per NHS England commissioning policy.
- Subgroup analyses by patient characteristics that affect the costs or benefits of treatment, such as genotype, prior treatment experience, interferon eligibility and severity of disease.
- The impact of uncertainty in the effects of treatment on the costs and benefits of the optimal strategies.

- The level of investment in implementation warranted by the optimal strategies in each of the patient groups to increase treatment uptake.
- The relationship between treatment effectiveness (SVR) and costs to help inform future decisions on new treatments yet to be licensed.

7 Summary

New treatments for chronic hepatitis C have recently undergone or are currently undergoing appraisal of their value to the NHS in England and Wales by NICE. These appraisals raise a number of questions for NHS England on how to manage the implementation of the new treatments, given the lack of guidance on prioritisation, treatment sequences and watchful waiting, the impact of reduced onward transmission, the impact of the limited evidence base on costs and benefits and the opportunity costs of high cost medications affecting large populations. The review of the available evidence indicates that more research is needed to inform the implementation of the new drugs. Additional cost-effectiveness analysis, based on the NICE guidance and in collaboration with other research groups working in this area, can offer timely evidence on how to manage the implementation of NICE guidance in practice.

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9 Technical Appendix

9.1 Detail on additional analyses

9.1.1 Background and objective

Treatment duration, treatment efficacy and the range of alternative treatment options licensed and available within the NHS varies according to genotype, prior treatment experience, interferon eligibility and severity of disease (e.g. presence of cirrhosis). For these reasons, the net health impact of a particular treatment can differ within each subgroup, and so too the optimum treatment. As a result, the optimal treatment strategy for the population of patients infected with chronic hepatitis C will incorporate a number of decisions about which treatment to provide within each subgroup.

The net health benefit from treating chronic hepatitis C includes both direct and indirect components. The direct net health benefit consists of the health benefits to the patient from achieving sustained virologic response (SVR), the cost savings from preventing complications in the future and the increased costs from treatment. The indirect net health benefit consists of the health benefits and cost savings from reducing the risk of onward transmission and reinfection, through the reduction in the prevalence of hepatitis C. The magnitude of this benefit will depend on the nature of the epidemic, namely current prevalence of chronic hepatitis C, treatment rates, and the SVR rates achieved in each subgroup.

Ideally, the cost-effective treatment strategy would be determined in a model that incorporated both direct and indirect benefits and compared all possible treatment strategies for their net health benefits. However, the large number of subgroups and possible treatments renders this approach impractical. If we consider only 3 genotype groups (1, 3, or 4) x 3 types of disease severity (mild, moderate, cirrhotic) x 3 types of treatment status (treatment naïve, treatment experienced and interferon ineligible or intolerant) there are 36 possible subgroups. In each of these population subgroups, there are a variable number of relevant treatment treatments: pegylated interferon alpha in combination with ribavirin (PR), protease inhibitor (simeprevir, boceprevir or telaprevir) in combination with PR, direct acting antivirals in combination with PR (sofosbuvir, daclatasvir), interferon-free treatments (sofosbuvir with ledipasvir, simeprevir or daclatasvir), watchful waiting strategies and possible treatment sequencing strategies, such as trying patients on PR before switching non-responders and treatment failures to an interferon-free treatment.

9.1.2 Summary of proposed approach

We therefore propose a simpler two-stage approach to inform the cost-effective strategy in each subgroup in a way that includes the full net health benefit from treatment. At a first stage, a static model (developed by York) would be used to indicate the cost-effective treatment for each subgroup, considering only the direct net health benefit. This can be used to calculate the population direct net health benefit. At a second stage, a dynamic model (the Bristol model) would be used to provide an estimate of the total net health benefit, including both the direct and indirect benefits, by assuming that the most cost-effective treatment for each subgroup identified in stage 1 were utilised. The population net health benefit from preventing onward transmission is the difference between the total net health benefit obtained in stage 2 and the direct net health benefit for the population obtained in stage 1. The size of this difference will be conditional on the average efficacy of the treatment strategies (mean SVR rate) and their costs. The overall population indirect net health benefit or 'transmission benefit' could be apportioned to each subgroup according to its relative size. The amount by which this transmission benefit would be expected to change with an increase in SVR could be used to assess the sensitivity of the optimum treatment strategy within each subgroup to changes in the size of the indirect net health benefit.

9.1.3 Model characteristics

Treatment treatments

a) Characterise separate treatment treatments for all possible population subgroups covered by NICE recommendations defined by genotype, disease severity (mild, moderate and cirrhotic) and treatment status (treatment naïve, treatment experienced, interferon ineligible or intolerant).
b) Introduce a treatment sequence. This would consist of PR for all patients followed by an interferon-free treatment for those who did not respond to the first treatment. Where there are multiple interferon-free treatments licensed and available for a particular subgroup, select the option that is most cost-effective when used first-line (requires a first stage of analysis without treatment sequences).
c) Characterise a watchful waiting approach in which patients are only treated in the moderate stage (watchful waiting for mild patients).

Population

a) Characterise the patient population in the model to reflect the chronic hepatitis C population in England in terms of prevalence, genotype, stage of disease and treatment experience. The characteristics of the current population of people who inject drugs (PWIDs) should reflect this population in England (demographics, prevalence of hepatitis C, average duration of injection).
b) Characterise treatment uptake in the model as the current treatment uptake observed in England (this will be varied in the sensitivity analysis).

Other modifications

a) Incorporate age-dependent health-related quality of life decrements.
b) Allow for patients who failed treatment to be retreated. The possibility of retreatment gives rise to a number of questions:
    - How many re-treatment cycles can a patient have?
    - What would happen in clinical practice to patients who failed an interferon-free treatment? Would an alternative treatment be tried?

9.1.4 Detail on additional analyses

1) Evaluate the cost-effective strategy for each population subgroup defined by genotype, disease severity (mild, moderate and cirrhotic) and treatment status (treatment naïve, treatment experienced, interferon ineligible or intolerant). This involves running the static model and conducting an incremental comparison of net health benefits in each subgroup. Compare the full range of potential treatment options, including treatment sequencing and watchful waiting (watchful wait until moderate, watchful wait until cirrhotic), for each population subgroup.
2) Evaluate the additional benefits from reduced onward transmission and additional costs from reinfection by running the full model (i.e. the dynamic model) for the entire population in England and Wales. The initial strategies evaluated for each subgroup are the strategies deemed cost-effective in (1).
3) Obtain the additional net benefit at the population level of reduced onward transmission and reinfection by subtracting the population net benefit in (1) from the population net benefit in (2).
4) As sensitivity analysis, evaluate the relationship between changes in SVR and additional net benefit at the population level of reduced onward transmission and reinfection. In order to do

this, evaluate the net benefit of a hypothetical strategy with SVR rates varied in 5% increments from the base case in both the static and dynamic models.

Sensitivity analyses

1) Test the impact of assuming no improvement in health related quality of life for patients with mild disease who achieve SVR.
2) Test the impact of assuming increased treatment uptake.

9.2 Treatment cost calculations

9.2.1 Size of the patient population

The size of the patient population was obtained from Public Health England estimates, complemented with information from the manufacturer's submission on sofosbuvir (19, 25). Public Health England shared the latest estimates of the population size based on a population model of the chronic hepatitis C, using information on the number of people with end-stage liver disease, hepatocellular cancer and death from liver disease from Hospital Episode Statistics (HES) and Office of National Statistics (ONS) up to 2009 (25). Table 3 presents the size and structure of the patient population.

Table 3 Population with chronic hepatitis C (25)

People with chronic hepatitis C	Number of people
Mild chronic hepatitis C (treatment naïve)	92,214
Moderate chronic hepatitis C (treatment naïve)	49,939
Compensated cirrhosis chronic hepatitis C (treatment naïve)	4,726
People with mild disease who did not achieve SVR (treatment experienced)	4,807
People with moderate disease who did not achieve SVR (treatment experienced)	6,839
People with cirrhotic disease who did not achieve SVR (treatment experienced)	1,508
Total	160,032

The breakdown of the patient population by genotype and eligibility to interferon was obtained from the manufacturer's submission on sofosbuvir: 45% genotype 1, 7% genotype 2, 44% genotype 3 and 4% genotypes 4, 5 and 6; 11% unsuitable for interferon (19). For the treatment cost calculations, people with genotypes 4, 5 and 6 were considered a single group.

9.2.2 Treatment costs

The treatment (or drug acquisition) costs were obtained from the additional analyses undertaken by the evidence review group for the NICE TA of ledipasvir-sofosbuvir (see Table 1: Breakdown of the

total costs) (35). These estimates reflect the average treatment cost given the patient characteristics and response to treatment. A number of assumptions were required in order to use these costs in the treatment cost model: (i) the treatment costs for pegylated interferon with ribavirin for genotype 2 were assumed equivalent to genotype 3, (ii) the treatment costs of sofosbuvir with pegylated interferon and ribavirin for genotype 3 were assumed equivalent to those for genotype 1, and (iv) the treatment costs of interferon ineligible people were assumed equivalent to treatment naïve people. Table 4 shows the treatment costs used in the treatment cost model.

Table 4 Treatment costs used in the treatment cost model

Genotype	Disease severity	Treatment status	Pegylated interferon with ribavirin (PR)	Telaprevir or Boceprevir with PR	Simeprevir with PR	Sofosbuvir with PR	Sofosbuvir with ribavirin	Ledipasvir-Sofosbuvir
1	Non-cirrhotic	Treatment naïve	£8,329	£26,721	£27,429	£37,072	N/A	£25,987
		Treatment experienced	£6,571	£29,612	£32,289	£37,072	N/A	£38,980
		Ineligible for interferon	N/A	N/A	N/A	N/A	N/A	£25,987
	Cirrhotic	Treatment naïve	£8,329	£27,987	£27,429	£37,072	N/A	£38,980
		Treatment experienced	£6,571	£29,612	£32,289	£37,072	N/A	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	N/A	£38,980
2	Non-cirrhotic	Treatment naïve	£3,907	N/A	N/A	N/A	N/A	N/A
		Treatment experienced	£3,907	N/A	N/A	N/A	£36,093	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	£36,093	N/A
	Cirrhotic	Treatment naïve	£3,907	N/A	N/A	N/A	N/A	N/A
		Treatment experienced	£3,907	N/A	N/A	N/A	£36,093	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	£36,093	N/A
3	Non-cirrhotic	Treatment naïve	£3,907	N/A	N/A	N/A	N/A	N/A
		Treatment experienced	£3,907	N/A	N/A	£37,072	N/A	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	N/A	N/A
	Cirrhotic	Treatment naïve	£3,907	N/A	N/A	£37,072	N/A	N/A
		Treatment experienced	£3,907	N/A	N/A	£37,072	N/A	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	£72,068	N/A
4	Non-cirrhotic	Treatment naïve	£8,329	N/A	£27,429	£37,072	N/A	N/A
		Treatment experienced	£6,571	N/A	£32,289	£37,072	N/A	£38,980
		Ineligible for interferon	N/A	N/A	N/A	N/A	N/A	£38,980
	Cirrhotic	Treatment naïve	£8,329	N/A	£27,429	£37,072	N/A	£38,980

		Treatment experienced	£6,871	N/A	£32,289	£37,072	N/A	N/A
		Ineligible for interferon	N/A	N/A	N/A	N/A	N/A	£38,980

9.3 Treatment cost calculations: full results

Tables 5 and 6 show the full results by genotype, disease severity and treatment status for the four scenarios considered for 3%(25) and 100% treatment uptake.

Table 5 Treatment cost assuming 3% treatment uptake (25)

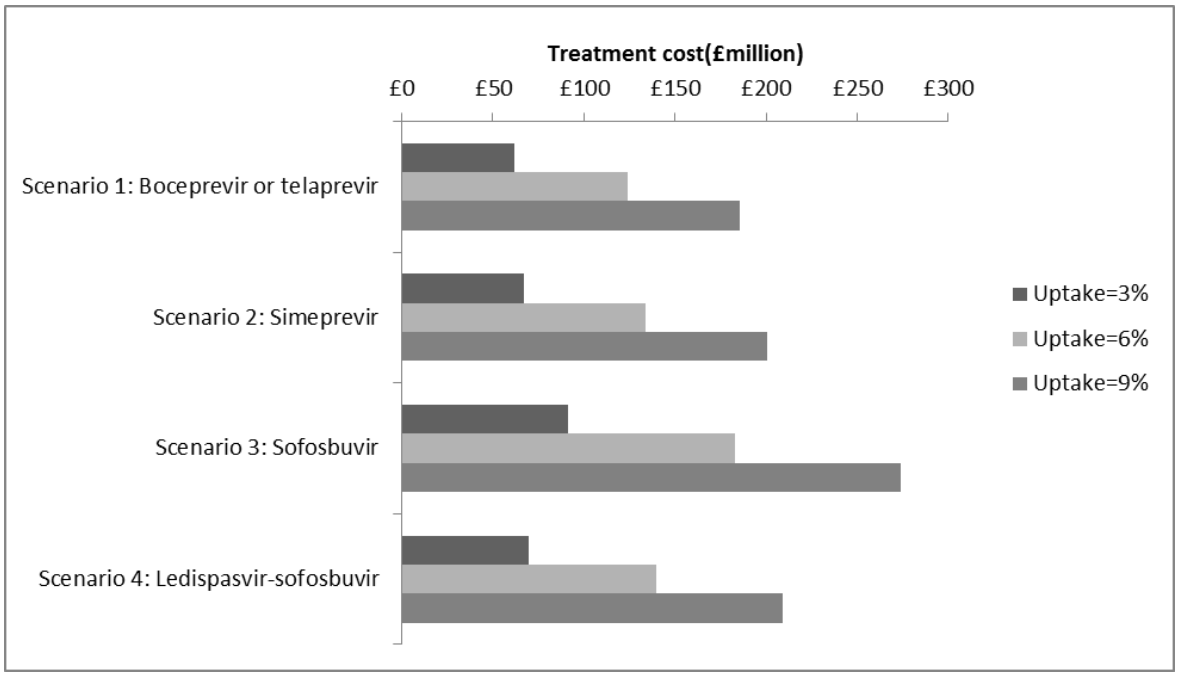
Genotype	Disease severity	Treatment status	Scenario 1: Boceprevir and Telaprevir	Scenario 2: Simeprevir	Scenario 3: Sofosbuvir	Scenario 4: Ledipasvir-Sofosbuvir
1	Non-cirrhotic	Treatment naïve	£45,743,677	£46,955,839	£63,463,354	£44,487,159
		Treatment experienced	£4,152,968	£4,528,345	£5,199,112	£5,466,716
		Ineligible for interferon	£0	£0	£0	£5,824,578
	Cirrhotic	Treatment naïve	£1,592,945	£1,561,171	£2,110,007	£2,218,612
		Treatment experienced	£537,600	£586,193	£673,023	£119,292
		Ineligible for interferon	£0	£0	£0	£354,119
2	Non-cirrhotic	Treatment naïve	£1,085,092	£1,085,092	£1,085,092	£1,085,092
		Treatment experienced	£88,894	£88,894	£821,141	£88,894
		Ineligible for interferon	£0	£0	£1,312,326	£0
	Cirrhotic	Treatment naïve	£36,074	£36,074	£36,074	£36,074
		Treatment experienced	£11,506	£11,506	£106,296	£11,506
		Ineligible for interferon	£0	£0	£53,191	£0
3	Non-cirrhotic	Treatment naïve	£6,510,555	£6,510,555	£6,510,555	£6,510,555
		Treatment experienced	£533,365	£533,365	£5,060,469	£533,365
		Ineligible for interferon	£0	£0	£0	£0
	Cirrhotic	Treatment naïve	£216,443	£216,443	£2,053,740	£216,443
		Treatment experienced	£69,038	£69,038	£655,076	£69,038
		Ineligible for interferon	£0	£0	£637,248	£0
4	Non-cirrhotic	Treatment naïve	£1,235,688	£4,069,506	£1,235,688	£1,235,688
		Treatment experienced	£79,866	£392,457	£79,866	£473,782
		Ineligible for interferon	£0	£0	£0	£757,185
	Cirrhotic	Treatment naïve	£41,084	£135,301	£182,867	£192,280
		Treatment experienced	£10,811	£50,803	£58,329	£10,811
		Ineligible for interferon	£0	£0	£0	£30,690
Total cost			£61,945,606	£66,830,584	£91,333,455	£69,721,879

Table 6 Treatment cost assuming 100% treatment uptake

Genotype	Disease severity	Treatment status	Scenario 1: Boceprevir and Telaprevir	Scenario 2: Simeprevir	Scenario 3: Sofosbuvir	Scenario 4: Ledipasvir-Sofosbuvir
1	Non-cirrhotic	Treatment naïve	£1,524,789,229	£1,565,194,646	£2,115,445,126	£1,482,905,300
		Treatment experienced	£138,432,255	£150,944,835	£173,303,721	£182,223,854
		Ineligible for interferon	£0	£0	£0	£194,152,613
	Cirrhotic	Treatment naïve	£53,098,162	£52,039,038	£70,333,571	£73,953,718
		Treatment experienced	£17,920,005	£19,539,754	£22,434,104	£3,976,385
		Ineligible for interferon	£0	£0	£0	£11,803,953
2	Non-cirrhotic	Treatment naïve	£36,169,748	£36,169,748	£36,169,748	£36,169,748
		Treatment experienced	£2,963,136	£2,963,136	£27,371,382	£2,963,136
		Ineligible for interferon	£0	£0	£43,744,194	£0
	Cirrhotic	Treatment naïve	£1,202,464	£1,202,464	£1,202,464	£1,202,464
		Treatment experienced	£383,546	£383,546	£3,543,215	£383,546
		Ineligible for interferon	£0	£0	£1,773,042	£0
3	Non-cirrhotic	Treatment naïve	£217,018,490	£217,018,490	£217,018,490	£217,018,490
		Treatment experienced	£17,778,817	£17,778,817	£168,682,288	£17,778,817
		Ineligible for interferon	£0	£0	£0	£0
	Cirrhotic	Treatment naïve	£7,214,782	£7,214,782	£68,458,010	£7,214,782
		Treatment experienced	£2,301,279	£2,301,279	£21,835,861	£2,301,279
		Ineligible for interferon	£0	£0	£21,241,606	£0
4	Non-cirrhotic	Treatment naïve	£41,189,605	£135,650,203	£41,189,605	£41,189,605
		Treatment experienced	£2,662,194	£13,081,886	£2,662,194	£15,792,734
		Ineligible for interferon	£0	£0	£0	£25,239,516
	Cirrhotic	Treatment naïve	£1,369,457	£4,510,050	£6,095,576	£6,409,322
		Treatment experienced	£360,354	£1,693,445	£1,944,289	£360,354
		Ineligible for interferon	£0	£0	£0	£1,023,009
		Total cost	£2,064,853,523	£2,227,686,118	£3,044,448,485	£2,324,062,624

Figure 5 compares the treatment cost with the current treatment uptake (3%(25)) to the impact of doubling (6%) and tripling (9%) uptake for each of the scenarios considered. The treatment cost of treatment is sensitive to treatment uptake.

Figure 5 Treatment cost of scenarios 1-4 for current, double and triple the current uptake



9.4 Comparison of NICE TAs on simeprevir, sofosbuvir and ledipasvir-sofosbuvir

Tables 8-16 summarise the costs-effectiveness results and NICE recommendations of the NICE TAs on simeprevir, sofosbuvir and ledipasvir-sofosbuvir (1-3).

Table 7 Cost-effectiveness results that informed NICE TA331 on simeprevir (1)

Genotype	Disease severity		***Treatment-naïve***		***Treatment experienced***					
					Interferon-eligible			intolerant to or ineligible for interferon treatment		
			Interferon-eligible	Interferon ineligible	*non responder*	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Genotype 1	Cirrhotic and non cirrhotic		SMV+PR (12 weeks plus further 12 weeks PR) vs PR (48 weeks): £14,200/QALY	SMV+SOF to be evaluated in a separate guidance once data are more mature	SMV+PR (12 weeks plus further 12 weeks PR) vs PR (48 weeks): £9,800/QALY			SMV+SOF to be evaluated in a separate guidance once data are more mature		
			SMV+PR (12 weeks plus further 12 weeks PR) vs BOC+PR (PR alone for 4 weeks then BOC+PR further 32 weeks then PR for further 12 weeks): Dominant		SMV+PR (12 weeks plus further 12 weeks PR) vs BOC+PR (PR alone for 4 weeks then BOC+PR further 32 weeks then PR for further 12 weeks): Dominant					
			SMV+PR (12 weeks plus further 12 weeks PR) vs TVR+PR (TVR/PR 12 weeks + 36 weeks PR only): Dominant		SMV+PR (12 weeks plus further 12 weeks PR) vs TVR+PR (TVR/PR 12 weeks + 36 weeks PR only): Dominant					
	Non cirrhotic	mild	Analysis not conducted for this appraisal							
		moderate	Analysis not conducted for this appraisal							
	Compensated cirrhosis		Analysis not conducted for this appraisal							
	Pre/post liver transplant		Analysis not conducted for this appraisal							
	HIV co-infected		Analysis not conducted for this appraisal							
Genotype 4	Cirrhotic and non cirrhotic		SMV+PR (12 weeks plus further 12 weeks PR) vs PR (48 weeks): £11,700/QALY	SMV+SOF to be evaluated in a separate guidance once data are more mature	SMV+PR (12 weeks plus further 12 weeks PR) vs PR (48 weeks): £8,900/QALY			SMV+SOF to be evaluated in a separate guidance once data are more mature		
	Non cirrhotic	mild	Analysis not conducted for this appraisal							
		moderate	Analysis not conducted for this appraisal							
	Compensated cirrhosis		Analysis not conducted for this appraisal							
	Pre/post liver transplant		Analysis not conducted for this appraisal							
	HIV co-infected		Analysis not conducted for this appraisal							

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 8 Cost-effectiveness results that informed NICE TA330 on sofosbuvir for genotype 1 (2)

<table>
<tr><td colspan="2" rowspan="3">Disease severity</td><td colspan="3">Treatment naive</td><td colspan="6">Treatment experienced</td></tr>
<tr><td rowspan="2">Interferon-eligible</td><td rowspan="2">Interferon ineligible</td><td colspan="3">Interferon-eligible</td><td colspan="3">intolerant to or ineligible for interferon treatment</td></tr>
<tr><td>non responder</td><td>partial responder</td><td>null responder</td><td>non responder</td><td>partial responder</td><td>null responder</td></tr>
<tr><td colspan="2" rowspan="3">Cirrhotic and non cirrhotic</td><td>SOF+PR(12 weeks) vs PR(48 weeks): £17,500/QALY</td><td rowspan="3">SOF+RBV(24 weeks) vs no treatment: £47,600 per QALY</td><td colspan="3">SOF+PR(12 weeks) vs PR(48 weeks): £12,600/QALY</td><td colspan="3" rowspan="3">The starting point for the Committee was the ICER of £47,600 per QALY gained (that is the ICER vs no treatment for people with genotype 1 treatment-naive HCV for whom interferon is unsuitable). Assuming that the relative difference between the ICERs in the treatment naive and treatment experienced HCV groups seen in other genotypes also applies to genotype 1 HCV, the Committee would expect that the ICERs for the genotype 1 treatment-experienced HCV group would likely be slightly lower than the ICER for people in the genotype 1 treatment-naive HCV group.</td></tr>
<tr><td>SOF+PR(12 weeks) vs BOC + PR(response-guided): £10,300/QALY</td><td colspan="3">SOF+PR(12 weeks) vs BOC+ PR(response-guided): £700/QALY</td></tr>
<tr><td>SOF+PR(12 weeks) vs Tel plus PR(response-guided): £15,400/QALY</td><td colspan="3">SOF+PR(12 weeks) vs Tel plus PR(response-guided): £8,200/QALY</td></tr>
<tr><td rowspan="2">Non cirrhotic</td><td>mild</td><td rowspan="2">SOF+PR(12 weeks) vs PR(48 weeks): £25,200/QALY</td><td rowspan="3">SOF+RBV(24 weeks) vs no treatment: £51,500 per QALY</td><td colspan="3" rowspan="3">Analysis not conducted for this appraisal</td><td colspan="3" rowspan="4">When stratified by the presence or absence of cirrhosis, the ICERs would be likely to increase in the subgroup without cirrhosis and decrease in the subgroup with cirrhosis in a similar proportion to that seen in the subgroup of people with treatment-naive genotype 1 HCV for whom interferon is unsuitable. However, the ICERs would still remain high.</td></tr>
<tr><td>moderate</td></tr>
<tr><td rowspan="2">Non cirrhotic</td><td>mild</td><td rowspan="2">SOF+PR(12 weeks) vs BOC + PR(response-guided): £14,300/QALY</td></tr>
<tr><td>moderate</td></tr>
<tr><td rowspan="2">Non cirrhotic</td><td>mild</td><td rowspan="2">SOF+PR(12 weeks) vs Tel plus PR(response-guided): £15,400/QALY</td><td rowspan="2">SOF+RBV(24 weeks) vs no treatment: £35,800 per QALY</td></tr>
<tr><td>moderate</td></tr>
<tr><td colspan="2" rowspan="3">Compensated cirrhosis</td><td>SOF+PR(12 weeks) vs PR(48 weeks): £5,400/QALY</td><td colspan="3" rowspan="3">Analysis not conducted for this appraisal</td></tr>
<tr><td>SOF+PR(12 weeks) vs BOC + PR(response-guided): £2,800/QALY</td></tr>
<tr><td>SOF+PR(12 weeks) vs Tel plus PR(response-guided): £4,200/QALY</td></tr>
<tr><td colspan="2">Pre/post liver transplant</td><td>N/A</td><td colspan="6">Analysis not conducted for this appraisal</td></tr>
<tr><td colspan="2" rowspan="2">HIV co-infected</td><td>SOF+PR(12 weeks) vs PR(48 weeks): £43,800/QALY</td><td colspan="6">Analysis not conducted for this appraisal</td></tr>
<tr><td>SOF+RBV(24 weeks) vs no treatment: £23,500 per QALY</td><td colspan="6">Analysis not conducted for this appraisal</td></tr>
</table>

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 9 Cost-effectiveness results that informed NICE TA330 on sofosbuvir for genotype 2 (2)

Disease severity	***Treatment-naïve***		***Treatment experienced***					
	Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
			non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Cirrhotic and non-cirrhotic		SOF+RBV (24 weeks) vs PR(48 weeks): £46,300/QALY	SOF+RBV (24 weeks) vs no treatment: £8,200 per QALY			"SOF+RBV (24 weeks) vs PR(48 weeks): £12,500		
Non cirrhotic	Analysis not conducted for this appraisal							
Compensated cirrhosis	Analysis not conducted for this appraisal							
Pre/post liver transplant	Analysis not conducted for this appraisal							
HIV co-infected	SOF+RBV (24 weeks) vs PR(48 weeks): £55,900/QALY	Analysis not conducted for this appraisal	SOF+RBV (24 weeks) vs PR(48 weeks): £128,200/QALY			SOF+RBV (24 weeks) vs no treatment: £10,600 per QALY		

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 10 Cost-effectiveness results that informed NICE TA330 on sofosbuvir for genotype 3 (2)

Disease severity		***Treatment- naïve***		***Treatment experienced***					
		Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
				non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Cirrhotic and Non-cirrhotic		SOF+PR(12 weeks) vs PR(48 weeks): £21,900/QALY	SOF+RBV (24 weeks) vs no treatment: £21,000 per QALY	SOF+PR(12 weeks) vs PR(48 weeks): £13,900/QALY			SOF+RBV (24 weeks) vs no treatment: £27,500 per QALY		
Non cirrhotic	Mild	SOF+PR(12 weeks) vs PR(48 weeks): £40,600/QALY	SOF+RBV (24 weeks) vs no treatment: £28k-32k per QALY	SOF+PR(12 weeks) vs PR(48 weeks): £18,600/QALY			SOF+RBV (24 weeks) vs no treatment: £31,4k-35k per QALY		
	Moderate								
Compensated cirrhosis		SOF+PR(12 weeks) vs PR(48 weeks): £6,600/QALY	SOF+RBV (24 weeks) vs no treatment: £10,5k-15,1k per QALY	SOF+PR(12 weeks) vs PR(48 weeks): £6,300/QALY			SOF+RBV (24 weeks) vs no treatment: £19,2k-29,7k per QALY		
Pre/post liver transplant		Analysis not conducted for this appraisal							
HIV co-Infected		SOF+PR(12 weeks) vs PR(48 weeks): dominant	N/A	SOF+PR(24 weeks) vs PR(48 weeks): £90,800/QALY			SOF+RBV (24 weeks) vs no treatment: £10,600 per QALY		

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 11 Cost-effectiveness results that informed NICE TA330 on sofosbuvir for genotype 4, 5 and 6 (2)

Disease severity		***Treatment naive***		***Treatment experienced***					
				Interferon-eligible			intolerant to or ineligible for interferon treatment		
		Interferon-eligible	Interferon ineligible	*non responder*	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Cirrhotic and Non-cirrhotic		SOF+PR(12 weeks) vs PR(48 weeks): £26,800/QALY	No evidence provided. Starting point £26,800/QALY but it is likely to be higher	SOF+PR(12 weeks) vs PR(48 weeks): starting point £26,800/QALY but might be slightly lower (high uncertainty)			It is likely to be substantially higher than £26,800 per QALY		
Non cirrhotic	mild Moderate	The Committee considered that, potentially the ICERs for both the cirrhotic and non-cirrhotic subgroups were likely to be high. The Committee also noted that if the ERG's exploratory assumptions were applied, it was likely the ICERs would increase further.							
Compensated cirrhosis									
Pre/post liver transplant									

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 12 Cost-effectiveness results that informed NICE TA on ledipasvir-sofosbuvir for genotype 1 (3)

Disease severity		*Treatment naive*		*Treatment experienced*					
		Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
				non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Non cirrhotic	mild	LED+SOF (12 weeks) vs SMV+PR (12 weeks plus further 12 weeks PR): £22,700/QALY. LED+SOF (8 weeks) vs SMV+PR(12 weeks plus further 12 weeks PR): dominant LED+SOF (8 weeks) vs PR(48 weeks): £9,000/QALY	Analysis not conducted for this appraisal	LED+SOF (12 weeks) vs no treatment: £16,600/QALY LED+SOF (12 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR): dominant LED+SOF (24 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR): £77,500/QALY			Analysis not conducted for this appraisal		
	moderate								
Compensated cirrhosis		LED+SOF (24 weeks) vs SIM+PR(12 weeks plus further 12 weeks Peg-α + Rib): £45,400/QALY LED+SOF (12 weeks) vs no treatment: £4,500/QALY	Analysis not conducted for this appraisal	LED+SOF (12 weeks) vs SIM+PR(12 weeks plus further 12 weeks Peg-α + Rib): £32,500/QALY			Analysis not conducted for this appraisal		
Pre/post liver transplant		Analysis not conducted for this appraisal							
HIV co-infected		Analysis not conducted for this appraisal							

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 13 Cost-effectiveness results that informed NICE TA on ledipasvir-sofosbuvir for genotype 3 (3)

Disease severity		*Treatment naive*		*Treatment experienced*					
		Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
				non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Non cirrhotic	mild	LED+SOF (12 weeks) vs SMV+PR(12 weeks plus further 12 weeks Peg-α + Rib): £88,900	Analysis not conducted for this appraisal	Analysis not conducted for this appraisal			LED+SOF+RBV(24 weeks) vs no treatment: £33,600/QALY		
	moderate								

Disease severity	***Treatment naive***		***Treatment experienced***					
	Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
			non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Compensated cirrhosis	LED+SOF+ Rib (24 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR : £46,100/QALY	Analysis not conducted for this appraisal	LED+SOF+RBV (24 weeks) vs SOF+RBV (24 weeks) £18,200-£30,500/QALY (high uncertainty)			Analysis not conducted for this appraisal		
Pre/post liver transplant	Analysis not conducted for this appraisal							
HIV co-infected	Analysis not conducted for this appraisal							

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 14 Cost-effectiveness results that informed NICE TA on ledipasvir-sofosbuvir for genotype 4 (3)

Disease severity		***Treatment naive***		***Treatment experienced***					
		Interferon-eligible	Interferon ineligible	Interferon-eligible			intolerant to or ineligible for interferon treatment		
				non responder	*partial responder*	*null responder*	*non responder*	*partial responder*	*null responder*
Non cirrhotic	mild	LED+SOF (12 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR): £22,700/QALY	Analysis not conducted for this appraisal	LED+SOF (12 weeks) vs no treatment: £16,600/QALY LED+SOF (12 weeks) vs SMV+PR(12 weeks plus further 12 weeks PR): dominant LED+SOF (24 weeks) vs SMV+PR(12 weeks plus further 12 weeks PR): £77,500/QALY			Analysis not conducted for this appraisal		
	moderate								
Compensated cirrhosis		LED+SOF (24 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR): £45,400/QALY	Analysis not conducted for this appraisal	LED+SOF (12 weeks) vs SIM+PR(12 weeks plus further 12 weeks PR): £32,500/QALY			Analysis not conducted for this appraisal		
Pre/post liver transplant		Analysis not conducted for this appraisal							
HIV co-infected		Analysis not conducted for this appraisal							

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 15 SVR estimates used for NICE TA331 on simeprevir (1)

Genotype 1	SVR (%)
Treament naïve	
PR (F0-F2)	51.9%
PR (F3)	35.4%
PR (F4)	35.4%
SMV+PR (OR vs PR)	4.83
TVR+PR (OR vs PR)	3.79
BOC+PR (OR vs PR)	3.54
Treatment experienced (relapsers)	
PR	26.5%
SMV+PR (OR vs PR)	9.02
TVR+PR (OR vs PR)	8.38
BOC+PR (OR vs PR)	7.18
Treatment experienced (partial responders)	
PR	10.9%
SMV+PR (OR vs PR)	8.73
TVR+PR (OR vs PR)	8.38
BOC+PR (OR vs PR)	7.18
Treatment experienced (null responders)	
PR	9.2%
SMV+PR (OR vs PR)	8.73
TVR+PR (OR vs PR)	8.38
BOC+PR (OR vs PR)	7.18
Genotype 4	
Treatments naïve	
PR (F3-F4)	0%
SMV+PR	61.6%
TVR+PR (OR vs PR)	61.6%
BOC+PR (OR vs PR)	41.6%
Treatments experiences (nulls)	
PR (F3-F4)	0%
SMV+PR	35.1%
TVR+PR (OR vs PR)	27.9%
BOC+PR (OR vs PR)	38.1%

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.; OR: Odds ratio

Table 16 SVR estimates used for NICE TA33 on sofosbuvir (2)

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+ PR	12	91.7	80.8	SVR-12	NEUTRINO
PR	48	43.6	23.6	SVR-24	McHutchison et al 2009
TVR+PR	48	75.4	61.9	SVR-24	Telaprevir NICE STA
BOC+PR	48	64.1	55.0	SVR-24	Lawitz et al 2012
HCV genotype 1, treatment naive, unsuitable for interferon					
SOF+RBV	24	67.6	36.4	SVR-12	QUANTUM and SPARE
No treatment		0	0	0	
HCV genotype 2, treatment naive, interferon eligible					
SOF+RBV	12	96.7	85.7	SVR-12	VALENCE and FISSION
PR	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; Shoeb et al

					2011
No treatment		0	0		
RBV	12	92.0	92.0	SVR-12	VALENCE and POSITRON
No treatment		0	0		
HCV genotype 3, treatment naive, interferon eligible					
SOF+PR	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
PR	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					
SOF+PR	12	83.3	83.3	SVR-12	LONESTAR-2
SOF+RBV	24	85.0	60.0	SVR-12	VALENCE
PR	48	35.0	35.0	SVR-24	Lagging et al 2013; Shoeb et al 2011
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+ PR	12	100	50.0	SVR-12	NEUTRINO
PR	48	50.0	38.6	SVR-24	Manns et al 2001

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 17 SVR estimates used for NICE TA33 on sofosbuvir for people co-infected with hepatitis C and HIV (2)

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
PR	48	35.2	25.0	SVR-24	Labarga et al 2012 (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
PR	48	86.0	61.1	SVR-24	Labarga et al 2012 (PERICO)
HCV genotype 2 treatment experienced HCV/HIV co-infected					
SOF+RBV	12	92.3	100.0	SVR-12	PHOTON 1
PR	48	86.0	61.1	SVR-24	Labarga et al 2012 (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
PR	48	86.0	61.1	SVR-24	Labarga et al 2012 (PERICO)
HCV genotype 3 treatment experienced HCV/HIV co-infected					
SOF+RBV	24	100.0	80.0	SVR-12	PHOTON 1
PR	48	86.0	61.1	SVR-24	Labarga et al 2012 (PERICO)

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

Table 18 SVR estimates used for NICE TA on ledipasvir-sofosbuvir (3)

Treatment	SVR(%) non-cirrhotic patients	SVR(%) for cirrhotic patients	Source
HCV genotype 1, treatment-naive			
LED+SOF	97.0%	94.3%	ION-1 and *post hoc* analysis of ION-3
SOF+PR	91.7%	80.8%	NEUTRINO
SMV+PR	82.0%	60.4%	Pooled data from studies QUEST and QUEST 2, taken from Simeprevir SPC 2014
TVR+PR	77.3%	53.4%	ADVANCE, ILLUMINATE and Grishchenko *et al*, 2009
BOC+PR	64.1%	55.0%	SPRINT-2
PR	43.6%	23.6%	IDEAL
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 4, treatment-naive			
LED-SOF	97.7%	94.3%	ION-1and *post hoc* analysis of ION-3
SOF+PR	91.7%	80.8%	NEUTRINO
SMV+PR	82.0%	60.4%	Pooled data from studies QUEST and QUEST 2, taken from Simeprevir SPC
PR	43.6%	23.6%	IDEAL
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 1 and genotype 4, treatment-experienced			
LED+SOF	95.6%	89.8%	ION-2
SOF+ PR	74.0%	74.0%	Pol et al, 2014
SMV+ PR	76.5%	66.7%	Pooled data from studies PROMISE and ASPIRE, taken from Simeprevir SPC 2014
TVR+ PR	72.2%	47.2%	REALIZE, taken from Telaprevir SmPC 2014
BOC+ PR	64.4%	35.3%	Bacon BR *et al*, 2011
PR	17.6%	10.0%	REALIZE, taken from Telaprevir SmPC, 2014
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 3, treatment-naive			
LED+SOF+RBV	100.0%	100.0%	ELECTRON-2
SOF+ PR	97.4%	83.3%	ELECTRON and PROTON
SOF+RBV (24 wks)	92.3%	-	VALENCE
PR (24 wks)	71.2%	29.7%	FISSION
HCV genotype 3, treatment-experienced			
LED+SOF+RBV	89.3%	77.3%	ELECTRON-2
SOF+RBV (24 wks)	87.0%	60.0%	VALENCE

PR: pegylated interferon with ribavirin; TVR/BOC+PR: telaprevir or boceprevir with pegylated interferon and ribavirin; SMV+PR: simeprevir with pegylated interferon and ribavirin; SOF+PR: sofosbuvir with pegylated interferon and ribavirin; SOF+RBV: sofosbuvir with ribavirin; SOF+LED: ledipasvir-sofosbuvir.

9.5 Comment on the opportunity cost of treatments for chronic hepatitis C

9.5.1 The opportunity costs from funding new interventions

The opportunity cost of funding new medications is the health forgone as a result of those resources being unavailable to fund other alternative competing priorities (32). Recent empirical research on the cost-effectiveness threshold to inform NICE decisions has estimated that the additional cost which results in 1 QALY being forgone by NHS patients is approximately £13,000 (31), lower than implied by the existing NICE threshold range. Furthermore, this research highlighted that technologies with non-marginal budget impacts on the NHS budget are likely to displace disproportionally more health, implying an even lower cost-effectiveness threshold. The opportunity cost considered by the National Institute for Health and Care Excellence (NICE) is represented by the NICE threshold, at £20,000 to £30,000 per quality-adjusted life year (QALY) gained (30). This suggests that when NICE approves medicines with ICERs close to £20,000 and/or that have a large budget impact, the services that are displaced may have generated more health for NHS users than that which is gained with the NICE approved therapy.

9.5.2 The opportunity costs of the new treatments for chronic hepatitis C

The new treatments for chronic hepatitis C represent a non-marginal budget impact given their high acquisition cost and large patient population. Assuming a budget impact between £300 million and £700 million per annum it is possible to describe the health that could have been generated with existing NHS services without those funds being diverted to new treatments for hepatitis C. The work that was undertaken to estimate the cost-effectiveness threshold also produced a calculator that would break down the impact on displaced services in terms of reduction in NHS spend per disease area and associated additional deaths, life years lost, total QALYs lost, QALYs lost due to premature death and QALYs lost due to reductions in health-related quality of life (32, 36).

Table 19 shows the health forgone from activities that are likely to be displaced elsewhere in the NHS from funding the new treatments assuming a budget impact of £300 million and £700 million using the opportunity cost calculator (36). Table 19 also shows the detailed breakdown of the disease areas where the health losses are likely to occur in the NHS. A budget impact of £300 million is associated with 1,542 additional deaths elsewhere in the NHS, which represent 6,989 years of life lost and 23,198 lost QALYs. A budget impact of £700 million is associated with 3,598 additional deaths elsewhere in the NHS, which represent 6,989 years of life lost and 54,128 lost QALYs. The new treatments for hepatitis C offer additional value to the NHS if their health benefits exceed the health losses elsewhere in the NHS. In other words, if the incremental cost-effectiveness ratio (ICER)

for NICE recommended hepatitis C treatment is less than £13,000, the health gains to patients receiving the new treatments for hepatitis C may exceed the health losses elsewhere in the NHS described in Table 19. However, and as discussed above, the large budget impact of the new treatments for chronic hepatitis C imply that the threshold may be lower than the £13,000 that underlies these calculations, and as such these may represent an underestimate of the health forgone. In addition, the breakdown of health losses across different disease areas may differ for non-marginal activities.

Table 19 Health forgone elsewhere in the NHS from funding the new treatments for chronic hepatitis C (36)

	Additional deaths		**Life years lost**		**Total QALYs lost**		**QALYs lost due to premature death**		**QALYs lost due to effects on quality of life**	
Budget impact (million)	£300	£700	£300	£700	£300	£700	£300	£700	£300	£700
Total	1,542	3,598	6,989	16,308	23,198	54,128	4,493	10,484	18,704	43,643
Cancer	112	262	1,125	2,625	790	1,843	732	1,707	58	136
Circulatory	683	1,595	3,479	8,118	3,235	7,548	2,211	5,159	1,024	2,389
Respiratory	401	936	482	1,124	6,881	16,055	302	704	6,579	15,350
Gastro-intestinal	78	183	740	1,726	1,317	3,072	485	1,132	831	1,940
Infectious diseases	22	50	159	372	470	1,097	108	252	363	846
Endocrine	20	47	149	348	1,817	4,240	97	227	1,720	4,013
Neurological	36	84	194	453	3,272	7,635	128	299	3,144	7,336
Genito-urinary	67	157	98	229	317	741	62	145	255	596
Trauma & injuries	-	-	-	-	-	-	-	-	-	-
Maternity & neonates	0	0	13	30	14	32	9	22	4	10
Disorders of Blood	11	26	50	116	655	1,529	34	79	621	1,450
Mental Health	85	198	385	899	2,858	6,669	249	582	2,609	6,087
Learning Disability	1	3	6	14	21	48	4	10	17	39
Problems of Vision	2	4	7	16	127	297	5	12	122	285
Problems of Hearing	1	2	4	10	420	981	3	7	417	973
Dental problems	0	0	0	1	204	476	0	0	204	475
Skin	7	17	33	78	58	136	21	50	37	86
Musculo-skeletal	12	27	53	124	696	1,625	35	81	662	1,544
Poisoning and AE	1	3	6	14	25	57	4	9	21	48
Healthy Individuals	1	2	5	11	20	47	3	7	17	40
Social Care Needs	-	-	-	-	-	-	-	-	-	-

9.5.3 Prioritisation strategies

NICE did not explicitly consider prioritisations strategies, such as watchful waiting and treatment sequencing. *Treatment sequencing* involves initially treating people with a less costly and less effective treatment (e.g. response guided pegylated interferon with ribavirin), then retreating people who do not achieve SVR (treatment failures) with more expensive and more effective treatment (e.g. ledipasvir-sofosbuvir or others). *Watchful waiting* consists of monitoring the patient until their disease progresses to a more severe stage then treating.

Watchful waiting strategies may be particularly cost-effective for patients with mild disease and a low likelihood of onward transmission. For example, it is estimated that 70% of patients will not develop cirrhosis, and among the 30% that do, time to progression is 40 years on average (3). If the aim of treatment is to reduce the incidence of events with a high health burden or health care costs (decompensated cirrhosis, end stage liver disease, liver transplant), then making new drugs available to all patients with chronic hepatitis C could represent overtreatment as up to 70% of those receiving high cost drugs would, in the absence of those drugs, have experienced little or no ill health consequences from their disease. An example of a watchful waiting strategy is making ledipasvir-sofosbuvir available for patients with METAVIR score F3 but not for patients at F2-F0. This issue was not discussed at the NICE committee meeting but has direct relevant to the value of the new treatments for chronic hepatitis C. The model for ledipasvir-sofosbuvir, for example, does not use METAVIR score and instead classifies the disease stages into cirrhotic and non-cirrhotic. Therefore, a new cost-effectiveness analysis which builds on NICE guidance to indicate the optimal strategy for each patient group is a priority for the NHS.

The questions about at what stage of disease progression is it cost-effective to treat and which treatment sequences offer the most value require further cost-effectiveness research. It is not possible to estimate the cost-effectiveness of watchful waiting and treatment sequencing strategies from the results of the NICE appraisals nor from the manufacturer's models submitted to NICE.