National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Sofosbuvir for treating chronic hepatitis C

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness *It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?*	Gilead Sciences	Hepatitis C Virus (HCV) is an area of high unmet need, with an estimated 160,000 people currently infected in England. Whilst HCV is a curable disease and there are treatments available that offer this possibility, significant safety/tolerability issues combined with variable success rates mean that only a small proportion of diagnosed patients are successfully treated each year. The burden of HCV is growing rapidly as patients infected with the disease in the 1980s and 1990s begin to develop serious complications. Health Protection England have estimated that whilst in the year 2000 there were 4,310 people with HCV related cirrhosis by 2010 this number had more than doubled to 9,670 and if left untreated this number would reach 15,840 by 2020. These data demonstrate how there is a growing public health need and burden to the NHS regarding HCV. Sofosbuvir (SOF) offers a step-change in efficacy, safety and tolerability for the treatment of patients, making successful HCV cure a realistic probability for a broader proportion of patients. In addition SOF provides a treatment option for many patients who currently have no option. It should be noted that the EMA has recently accepted an accelerated regulatory process for SOF, a designation only granted to those medicines of major public health interest. Gilead Sciences Ltd. fully supports SOF timely referral to and review by NICE. The best opportunity for cure with any patient is to treat as early as possible as increased fibrosis/cirrhosis correlates to poorer treatment	Comments noted. No changes required.

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		outcomes. For patients with advanced liver disease (it is estimated that 10,000 patients have HCV-related cirrhosis), the need to treat earlier becomes even more pressing; in particular, patients awaiting liver transplant may have no alternative treatment options to clear the HCV. Given the urgent need for those patients with life-threatening liver disease and no treatment options, Gilead Sciences Ltd. wishes to ensure that the timing of NICE guidance aligns with the accelerated regulatory review timelines for SOF. We therefore strongly support an STA submission in 2013 to support this alignment.	
	Royal College of Pathologists	There is a need for a different class of antiviral agent to treat chronic hepatitis C. Sofosbuvir fulfils this need and offers an interferon free option. It is appropriate for this agent to be referred for NICE appraisal.	Comments noted. No changes required.
	Foundation for Liver Research	The groups of patients studied should include genotype 1, 4 and 6 who have been previously treated and should also include the special group of HIV/HCV co-infection and HCV patients before and after liver transplantation.	Comments noted and raised at the scoping workshop. The Committee is only able to make recommendations on the use of a technology in line with its marketing authorisation. At the scoping workshop it was noted that people with chronic hepatitis C genotype 1, 4, 5 or 6 who have been previously treated were not included in the clinical trials, and therefore it was assumed that they would not be included as part of the marketing authorisation. Effect of treatment for people with HIV co-infection is currently included as a subgroup under other considerations in the scope and will be considered by

Section	Consultees	Comments	Action
			the Appraisal Committee if the evidence allows. No changes required.
	The Hepatitis C Trust	Extremely appropriate. This is the first new drug that will allow omission of interferon, albeit probably only in genotype 2. It has been eagerly anticipated by patients.	Comment noted. No changes required.
	Southampton Health Technology Assessments Centre (SHTAC)	Agree this topic is appropriate and relevant.	Comment noted. No changes required.
	Royal College of Nursing	We welcome the consultation on sofosbuvir for patients with HCV. It is fully appropriate to refer Sofosbuvir to NICE for appraisal in all genotypes as stated and particularly to assess the evidence in relation to genotype 1 treatment naïve populations and genotype 3 retreatment patients.	Comment noted. No changes required.
	UK Clinical Pharmacy Association	Yes appropriate for referral.	Comment noted. No changes required.
	Janssen	Janssen believes this is an appropriate topic to refer to NICE for appraisal.	Comment noted. No changes required.
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should*	Gilead Sciences	Yes the draft remit reflects the objective of the appraisal.	Comment noted. No changes required.
	Royal College of Pathologists	The wordings are appropriate.	Comment noted. No changes required.
	Foundation for Liver Research	This does not emphasise the benefits of oral administration and lack of side-effects as compared with Interferon therapy. The description of the technology does not emphasise the extraordinary results that are being	Comment noted. The remit defines the question that the Appraisal Committee will need

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consider? If not, please suggest alternative wording.		reported with this agent and the major breakthrough that oral treatment alone can give a high cure rate in hepatitis C. This transforms HCV treatment and the special groups of co-infection and liver transplantation and other difficult to treat groups will have a high chance of real benefit for the first time.	to answer, and is only intended to outline the indication and technology for appraisal. The background section of the scope and the technology section are only intended to provide a brief summary of the condition, existing treatments, and the technology. Detailed epidemiological information and a description of the technology and supporting clinical trial base will be included in the manufacturer's submission. No changes required.
	The Hepatitis C Trust	Yes	Comment noted. No changes required.
	Royal College of Nursing	The wording provided does reflect the issues of clinical outcomes and cost effectiveness in QALY. It may be worth reviewing these in cost per sustained virologic response (SVR) also. Recent data presented at EASL 2013 suggested a cost per SVR for Telaprevir was approximately $195k (£129K) in relation to the additional healthcare requirements and resources that patients need to complete treatment.	Comment noted. The Committee will assess the economic evidence presented in the manufacturer's submission and in the critique provided by the independent evidence review group. No changes required.
	Janssen	Janssen believes that the wording of the remit should reflect the anticipated licence.	Comment noted. No changes required.
	UK Clinical Pharmacy Association	Needs to emphasise the first time there is a possibility of interferon free regimens which will enable treatment of a population of patients that were unable to be treated due to contra-indications/intolerance to interferon.	The remit defines the question that the Appraisal Committee will need to answer, and is only intended to outline the indication and technology for appraisal.

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			The technology section of the scope is only intended to provide a brief summary of the technology. A detailed description of the technology and supporting clinical trial base will be included in the manufacturer's submission. No changes required.
Timing Issues *What is the relative urgency of this proposed appraisal to the NHS?*	Gilead Sciences	SOF is a medicine that offers a step-change in an area of high unmet and urgent need. The recent NHS Outcomes Framework has set a priority to reduce mortality due to liver disease in the under-75s. HCV is a significant driver for liver-related deaths (at least 296 in 2011) and a key driver for morbidity, with HCV-related cirrhosis and hepatocellular carcinoma (HCC) being life-threatening end stages of HCV disease. A substantial proportion of liver transplants performed in the UK are required as a result of advanced HCV infection. With around 10,000 UK patients living with HCV-related cirrhosis or HCC there is a significant group of patients whose health would be compromised by any delay to treatment. It is well established that increasing levels of cirrhosis and fibrosis leads to decreased likelihood of success with any therapy. Therefore delay to treatment for these patients will lead to increased mortality and morbidity. This means poorer outcomes for patients coupled with increased associated healthcare costs. SOF represents a breakthrough treatment for HCV, offering: • Superior clinical efficacy vs. NICE-recommended SoC (even amongst cirrhotic patients who are typically the most difficult to treat) • A side effect profile similar to placebo and superior to the current	Comment noted. No changes required.

Section	Consultees	Comments	Action
		SoC • Shorter treatment duration (from 24-48 weeks down to 12 weeks) with the opportunity for an IFN-free, all-oral treatment regime for GT2 and GT3 (this is particularly important for those patients unsuitable for IFN)	
	Gilead Sciences	The implications are as follows: • Significantly greater proportion of HCV patients can achieve a cure • Decreased treatment-emergent side effects and discontinuations compared to NICE-approved SoC – leading to decreased healthcare costs associated with managing the potentially severe side effects • Improved QoL for patients as demonstrated by a reduced treatment side effect profile and decreased duration of treatment • As this is an infectious disease with the potential for cure, by improving cure rates together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden to the NHS of HCV All of this means that there is an urgent need for timely patient access to SOF, re-iterating the need for timely NICE review and guidance. Given the urgent need for those patients with life-threatening liver disease and no treatment options, Gilead Sciences Ltd. wishes to ensure that the timing of NICE guidance aligns with the accelerated regulatory review timelines for SOF. We therefore strongly support an STA submission in 2013 to support this alignment.	Comment noted. This technology will be considered as a single technology appraisal (STA). No changes required.
	Royal College of Pathologists	Fairly urgent so as to provide timely guidance on the use of sofosbuvir when it is available.	Comment noted. No changes required.
	Foundation for	This is urgent as in America and throughout Europe, the drug will be	Comment noted. No changes

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	Liver Research	being used form the beginning of next year or before. It has been given priority consideration by the FDA.	required.
	Terrence Higgins Trust	Current treatments are effective 60% of the time. The improved efficacy of this treatment, in addition to the innovation in administration of the treatment, mean that it should be a priority to ensure the most effective treatment is available on the NHS and that NHS resources are used effectively.	Comment noted. No changes required.
	The Hepatitis C Trust	Extreme. Many patients have long been waiting for interferon-free/sparing treatment.	Comment noted. No changes required.
	Royal College of Nursing	As this for some offers the option of an all oral regimen which is well tolerated by most with minimal co-morbidities and good adherence and SVR rates in the genotype 1 and genotype 2 populations are promising. Given the potential to improve the quality of life of patients on treatment we consider that this should be reviewed.	Comment noted. No changes required.
	UK Clinical Pharmacy Association	Prompt appraisal post licensing will enable earliest possible use.	Comment noted. No changes required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information *Consider the accuracy and completeness of this information.*	Gilead Sciences	No comments	No changes required.
	Royal College of Pathologists	A reasonable short account of the current situation.	Comment noted. No changes required.
	The Hepatitis C Trust	End paragraph 3. 5 out of 6 are unaware of their infection is now out of date. It is either probably 3 or 4. I would say 'more than half are unaware of their infection'.	Comment noted. Scope update accordingly.
	Southampton	It would be useful to highlight that people with genotype 2 or 3 have a	Comment noted. Scope updated

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	Health Technology Assessments Centre (SHTAC)	better response to current [peginterferon and ribavirin] treatment than those with genotype 1 or 4.	accordingly.
	Royal College of Nursing	There are trials still in progress and pending following less than desired outcomes in G3 retreatment populations.	Comments noted. No changes required.
	Merck Sharp & Dohme (MSD)	The draft scope reports that 5 out of every 6 chronic hepatitis patients are unaware of their infection. However, the HPA report of Hepatitis C in the UK references the UAM survey which suggests that only 50% of participating people who inject drugs in England were aware of their HCV positive status. Reference: Hepatitis C in the UK 2012, Health Protection Agency We would suggest that the final paragraph of this section is re-worded to ensure clarity of which treatments are recommended by genotype: "*NICE guidance (TA75, TA106) recommends that standard treatment for the genotypes 2 to 6 with chronic hepatitis C, regardless of disease severity, is combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. For people with genotype 1 chronic hepatitis C, who have not been previously treated or who have been previously treated, NICE guidance recommends telaprevir in combination with peginterferon alfa and ribavirin (TA252) or boceprevir in combination with peginterferon alfa and ribavirin (TA253).*"	Comments noted. Scope updated accordingly. Comment noted. Please note that this suggested wording implies that TA200 has been replaced by the TA252 and TA253 recommendations, which is not the case. TA 252 and TA253 offer additional treatment options for people with genotype 1 chronic hepatitis C. No changes required.
	Children's HIV Association (CHIVA)	The statement regarding genotype 1 and 4 being ones with better response to treatment is not correct.	Comments noted. Scope updated accordingly.
The technology/ intervention	Gilead Sciences	'SOF is a first-in-class uridine nucleotide….' Gilead suggests the addition / amendment of the above underlined	Comments noted. The word 'nucleoside' has been changed to 'nucleotide' in the scope. The technology section is only intended

Section	Consultees	Comments	Action
Is the description of the technology or technologies accurate?		wording and agrees that the description is accurate.	to provide a brief description of the technology. More detailed information about the technology, such as the fact that it is 'first in class' will be included in the manufacturer's evidence submission.
	Royal College of Pathologists	Accurate.	Comments noted. No changes required.
	Southampton Health Technology Assessments Centre (SHTAC)	Please confirm what treatment duration will be considered?	Comments noted. Treatment duration will be determined during the regulatory process. The Appraisal Committee can only make recommendations on the use of the treatment in line with the marketing authorisation. No changes required.
	Royal College of Nursing	Yes.	Comments noted. No changes required.
	Janssen	Janssen suggests the description be changed to: Adults with genotype 1, 4, 5 and 6 • Sofosbuvir + Pegylated interferon alfa, with or without ribavirin. Adults with genotype 2 and 3 • Sofosbuvir, with or without ribavirin.	Comments noted and raised at the scoping workshop. The population in the scope has been updated as follows: For sofosbuvir in combination with peginterferon alfa and ribavirin: Adults with genotype 1, 4, 5 or 6 chronic hepatitis C For sofosbuvir in combination with ribavirin: Adults with genotype 2 or 3

Section	Consultees	Comments	Action
			chronic hepatitis C
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Gilead Sciences	**Genotypes** Earlier data with peginterferon/ribavirin have combined GT2 and GT3 together in clinical trials. Advances in understanding of HCV have resulted in the realisation that GT2 and GT3 have different responses to treatment. For this reason Gilead suggests that the populations are split out across genotypes (GT) as follows: GT1 GT2 GT3 GT4-6 **Treatment naïve (TN) – eligible for IFN / Treatment naïve (TN) – unsuitable for IFN / Treatment experienced (TE)** Gilead agrees that there are current Phase III clinical data relating to the following: GT1, GT4-6: TN GT2 GT3: TE and TN – for patients eligible for IFN and those unsuitable for IFN. **Cirrhotic / non-cirrhotic** It should be noted that, in order to best reflect real-world practice and to demonstrate efficacy in the most difficult to treat, Gilead Sciences Ltd. incorporated both cirrhotic and non-cirrhotic patients within the Phase III trial cohorts. Results presented will incorporate overall patient outcomes across both cirrhotic and non-cirrhotic populations.	Comments noted, and raised at the scoping workshop. It will be at the manufacturer's discretion how they would like to present the data by genotype in their evidence submission. The Committee will assess all of the clinical trial evidence submitted during the course of the appraisal to inform its decision on whether the technology should be recommended for use in line with the marketing authorisation (i.e. for the whole licenced population), or in specific subgroups where a significant clinical effect may be demonstrated. It will be at the manufacturer's discretion which subgroup analyses it presents in its evidence submission. No changes required.
	Royal College of Pathologists	Why are those patients with genotype 1, 4, 5 and 6 chronic hepatitis C who had previously been treated excluded from consideration?	Comments noted, and raised at the scoping workshop. Attendees at the scoping workshop agreed that this population should not be added to the scope as it is not included within the manufacturer's

Section	Consultees	Comments	Action
			trials and therefore will not be covered by the marketing authorisation. The Committee is only able to make recommendations on the use of the technology in line with its marketing authorisation. No changes required.
	Terrence Higgins Trust	If the numbers are sufficient we would recommend a sub group looking at HIV co-infections.	Comment noted. This subgroup is currently stated under other considerations in the scope and will be considered if evidence allows. No changes required.
	The Hepatitis C Trust	We would like to see added 'adults with genotype 1, 4, 5 and 6 who have previously been treated' if that is in the licence.	Comments noted, and raised at the scoping workshop Attendees at the scoping workshop agreed that this population should not be added to the scope as it is not included within the manufacturer's trials and therefore will not be covered by the marketing authorisation. The Committee is only able to make recommendations on the use of the technology in line with its marketing authorisation. No changes required.
	Southampton Health Technology Assessments Centre (SHTAC)	Please clarify if the population group will include: - only those with compensated HCV (i.e. exclude those with decompensated HCV)? - all severities of HCV (mild, moderate & severe)?	Comments noted and raised at the scoping workshop. It was agreed that the population would only include those with compensated cirrhosis as those with

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		- those who are co-infected with HIV?	decompensated cirrhosis were not included within the clinical trials. Attendees at the scoping workshop viewed the severities of hepatitis as being an outdated approach for classification and therefore suggested this was not defined. HIV co-infection is currently classed as a subgroup in the other considerations section of the scope and will be considered if the evidence allows. No changes required.
	Royal College of Nursing	For the most part, more genotype 3 retreatment population evidence is still required with and without Peg interferon.	Comment noted. No changes required.
	UK Clinical Pharmacy Association	Are previously treated genotype 1,4,5,6 patients deliberately excluded? Potential to include protease inhibitor treatment experienced genotype 1 patients.	Comments noted, and raised at the scoping workshop. It was agreed by attendees at the scoping workshop that the previously treated population with genotype 1, 4, 5 or 6 chronic hepatitis C should not be added to the scope as it is not included within the manufacturer's trials and therefore will not be covered by the marketing authorisation. The Committee is only able to make recommendations on the use of the technology in line with its marketing authorisation. Attendees at the scoping workshop also

Section	Consultees	Comments	Action
			discussed including a subgroup of people with genotype 1 hepatitis C who have previously been treated with protease inhibitors. It was agreed that this was a small population, for which there is unlikely to be robust clinical evidence, and therefore should not be included in the scope. No changes required.
	Children's HIV Association (CHIVA)	Please clarify the lower limit of age for 'adults' to be included in the appraisal. Would it be patients aged >16years? If so it may be relevant for paediatricians who often look after young people up to the age of 18.	Comments noted and raised at the scoping workshop. It was agreed by attendees, that the lower age should be 18 years, as this was the age cut off in the clinical trials. No changes required.
Comparators *Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	Gilead Sciences	Where peginterferon alfa is used, the standard of care for HCV treatment across the genotypes in the UK is peginterferon alfa plus ribavirin (peg/riba). All SOF trials (where appropriate) utilised results with peg/riba for comparison and the anticipated label is for use in combination with peg/riba. Therefore we suggest that only peg/riba is used as the comparator as opposed to peginterferon alfa +/- ribavirin. It should also be noted that for a significant proportion of patients there are no alternative treatment options (i.e. those who are unsuitable for interferon – such as those who are medically ineligible or those who are interferon-intolerant). For such patients the alternative is a 'no treatment' or placebo comparator (such as those patients included in certain SOF PhIII data). Gilead agrees that the two protease inhibitors, telaprevir or boceprevir, in combination with peg/riba would be appropriate comparators for genotype	Comments noted. Attendees at the scoping workshop discussed whether ribavirin was always used with peginteferon alfain clinical practice. It was recognised that in exceptional circumstances only, peginteferon alfa is used without ribavirin. Attendees at the scoping workshop discussed whether a 'no treatment' comparator should be included in the scope. They agreed that a best supportive care comparator should be included in the scope and that it should be defined as including treatments to manage the liver disease without a treatment for the hepatitis C.

Section	Consultees	Comments	Action
		1.	Scope has been updated to reflect this.
	Royal College of Pathologists	The comparators are the current standard.	Comment noted. No changes required.
	The Hepatitis C Trust	All the comparators should ONLY be 'with ribavirin'. That is the current SOC (with or without PIs) except for those intolerant of ribavirin – and they will not be able to take Sofosbuvir with ribavirin.	Comment noted, and raised at the scoping workshop. Attendees at the scoping workshop discussed whether ribavirin was always used with peginteferon alfa in clinical practice. It was recognised that in exceptional circumstances only peginteferon alfa is used without ribavirin.
	Southampton Health Technology Assessments Centre (SHTAC)	Will BSC be included as a comparator?	Comment noted and raised at the scoping workshop. Attendees at the workshop agreed that best supportive care should be included as a comparator in the scope and that it should be defined as including treatments to manage the liver disease without a treatment for the hepatitis C. Scope has been updated to reflect this.
	Royal College of Nursing	Yes.	Comments noted. No changes required.
	Janssen	Janssen suggests the description be changed to: Adults with genotype 1: • Peginterferon alfa with ribavirin • Telaprevir in combination with peginterferon alfa and ribavirin	Comment noted, and raised at the scoping workshop. Attendees at the scoping workshop discussed whether ribavirin was always used with peginteferon in clinical

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		• Boceprevir in combination with peginterferon alfa and ribavirin Adults with genotype 2,3,4,5 and 6: • Peginterferon alfa with or without ribavirin	practice. It was recognised that in exceptional circumstances only peginteferon alfa is used without ribavirin.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	Gilead Sciences	Gilead agrees with the main outcomes to be considered with the following additions: • Prevention of hepatocellular carcinoma (HCC) • Prevention of liver disease progression – e.g. cirrhosis • Prevention of liver transplant	Comments noted and raised at the scoping workshop. Attendees at the scoping workshop recognised that these outcomes would be useful for economic modelling but concluded that as they would not be able to be captured during the duration of any clinical trial, they should not be included as outcomes in the scope. However, the manufacturer is encouraged to provide evidence for additional outcome measures if it is available. No changes required.
	Royal College of Pathologists	It is desirable to further define the nature of the adverse effects of treatment – e.g anaemia, psychiatric symptoms, autoimmune disorders, dermatological problems etc.	Comment noted and raised at the scoping workshop. It was agreed by attendees at the workshop that the adverse event outcome listed in the scope should be kept broad to capture any potential adverse events. The manufacturer is encouraged to provide evidence on all adverse effects of treatment in its evidence submission. No changes required.
	Terrence Higgins Trust	We would encourage NICE to include reduced reinfection as an outcome and to expand the quality of life outcome beyond health. If Sofosbuvir is to	Comments noted. If evidence allows, the Committee will

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		be appraised after January 2014 outcomes including impact on ability to participate in employment/volunteering, improved independence, reduced reliance on social care and improved family/social life should also be factored in as the expectation is that medicines will be appraised beyond solely their health impact.	consider wider societal benefits of treatment. Previous technology appraisals for chronic hepatitis C have acknowledged the public health impact of treatment on reducing the onward transmission of HCV to uninfected people as a potential wider societal benefit. No changes required.
	Southampton Health Technology Assessments Centre (SHTAC)	Will the following outcomes be included: - virological relapse? - biochemical response? - histological response?	Comments noted and raised at the scoping workshop. Attendees at the scoping workshop agreed that these outcomes were historically used as surrogate outcomes for sustained virological response, and as this can now be measured accurately these outcomes are not required in this scope. No changes required.
	Royal College of Nursing	There may be sub groups that the current outcomes do not cover as there is no mention of disease level.	Comment noted. Attendees at the scoping workshop viewed the severities of hepatitis as being an outdated approach for classification and therefore suggested this was not defined. No changes required
	Merck Sharp & Dohme (MSD)	It is suggested that relapse rate is considered as an outcome measure.	Comment noted and raised at the scoping workshop. It was agreed by attendees at the workshop that relapse rate would be captured under sustained virological response and therefore no

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			changes are required.
	Janssen	Janssen would like some clarity around the definition of the outcome: Degree of virological response.	Comment noted and raised at the scoping workshop. It was recognised that degree of virological response was an important outcome for the appraisal of telaprevir and boceprevir as each of these agents could be stopped according to the level of virological response, which would impact cost effectiveness. It was agreed by attendees at the workshop that as the duration of treatment with sofosbuvir was not impacted by virological response, and therefore people would receive sofosbuvir for the full 12 weeks of treatment, this outcome was not relevant to this scope. This outcome has been removed from the scope accordingly.
Economic analysis *Comments on aspects such as the appropriate time horizon.*	Gilead Sciences	Gilead agrees that the time horizon should be such as to capture the full differences in costs or outcomes between the technologies being compared, and given the long term consequences / benefits a lifetime analysis is likely to be required.	Comments noted. No changes required.
	Royal College of Pathologists	No comments	No changes required.
	Terrence Higgins Trust	As per above costs should extend beyond NHS and personal social services and should consider other financial impacts on the individuals' and/or carers' increased ability to gain employment and the wider societal	Comments noted. No changes required.

Section	Consultees	Comments	Action
		impacts.	
	The Hepatitis C Trust	This should take account of the cost of onward transmission. Curing people prevents onward infection and this should be reflected in the ICER figure	Comments noted. If evidence allows, the Committee will consider wider societal benefits of treatment. Previous technology appraisals for chronic hepatitis C have acknowledged the public health impact of treatment on reducing the onward transmission of HCV to uninfected people as a potential wider societal benefit. No changes required.
	Southampton Health Technology Assessments Centre (SHTAC)	This is consistent with the scope of previous NICE appraisals of hepatitis C.	Comments noted. No changes required.
Equality and Diversity	Gilead Sciences	In addressing the appraisal NICE should be aware that HCV adversely affects certain populations who could be considered at risk of being disadvantaged in terms of accessing the healthcare system and therefore at risk of inequity of access to innovative new treatments. For example: - Certain immigrant populations - Prison population - Intravenous drug users	Comments noted. Attendees at the scoping workshop agreed that this issue related to implementation and could not be addressed through technology appraisal recommendations. No changes required.
	Royal College of Pathologists	No issues	Comments noted. No changes required.
	Southampton Health Technology Assessments	No comments	Comments noted. No changes required.

Section	Consultees	Comments	Action
	Centre (SHTAC)		
Innovation *Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal*	Gilead Sciences	SOF meets the 5 criteria for step-change innovation as laid out by the Kennedy Report, such that: • SOF significantly and substantially improves the way that a current need is met (*superior clinical efficacy vs. NICE-recommended SoC coupled with a placebo-like side effect profile and a new treatment option for the significant proportion of GT2 and GT3 patients unsuitable for interferon*) • SOF meets a need which the NHS has identified as being important (*the recent NHS Outcomes Framework reflects the government commitment to reducing mortality due to liver disease in the under-75s*) • SOF has a robust evidence set providing research on the populations in which the product is effective (*clinical trials across the GTs and incorporating relevant subgroups*) • SOF has demonstrated an appropriate level of effectiveness (*superior clinical efficacy vs. NICE-recommended SoC – and an increase in the proportion of patients suitable for treatment*) • SOF will have a marketing authorisation for the indication under review In further detail, SOF represents a breakthrough treatment for HCV, offering: • Superior clinical efficacy vs. NICE-recommended SoC (even amongst cirrhotic patients who are typically the most difficult to treat) • A side effect profile similar to placebo and superior to the current SoC • Shorter treatment duration (from 24-48 weeks down to 12 weeks) with the opportunity for an IFN-free, all-oral treatment regime for	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir in its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.

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Committee to take account of these benefits.		GT2 and GT3 (this is particularly important for those patients unsuitable for IFN)	
	Gilead Sciences	The implications are as follows: • Significantly greater proportion of HCV patients can achieve a cure • Decreased treatment-emergent side effects and discontinuations compared to NICE-approved SoC – leading to decreased healthcare costs associated with managing the potentially severe side effects • Improved QoL for patients as demonstrated by a reduced treatment side effect profile and decreased duration of treatment • As this is an infectious disease with the potential for cure, by improving cure rates together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden to the NHS of HCV All of this means that there is an urgent need for timely patient access to SOF, re-iterating the need for timely NICE review and guidance. Given the urgent need for those patients with life-threatening liver disease and no treatment options, Gilead Sciences Ltd. wishes to ensure that the timing of NICE guidance aligns with the accelerated regulatory review timelines for SOF. We therefore strongly support an STA submission in 2013 to support this alignment. Health related benefits that are unlikely to be included in the QALY calculation include the reduction in onward transmission of the hepatitis C virus through rapid clearance of the virus from the body due to effective treatment, together with the potential for reversal of liver fibrosis once cured of HCV.	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir, including any health-related benefits that are inadequately captured in the QALY calculation in its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	Gilead Sciences	<u>Onward transmission</u> Data to support this are the rapid reductions in HCV RNA to <LLOQ (lower limit of quantitation) regardless of GT and which are sustained post-	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir, including any health-

Section	Consultees	Comments	Action
		treatment in the majority of patients (as per the clinical trials) together with public health information re: rates of transmission from individuals infected with HCV. As this is an infectious disease with the potential for cure, by improving cure rates together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden to the NHS of HCV. Therefore additional benefits exist from a public health perspective that are not fully captured in the QALY calculation <u>Reversal of liver fibrosis</u> HCV cure (or SVR) may result in the reversal of fibrosis and regression of cirrhosis with a reduction in all-cause mortality. These health-related benefits are unlikely to be fully captured in the QALY calculation	related benefits that are inadequately captured in the QALY calculation in its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	Royal College of Pathologists	This technology is expected to provide a step change in current management.	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	Foundation for Liver Research	The new oral and highly effective anti-HCV drugs can only considered as greatly innovative.	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	Terrence Higgins Trust	This is a highly innovative treatment which is administered orally unlike current treatments which are all injections.	Comments noted. The manufacturer is encouraged to

Section	Consultees	Comments	Action
		Additionally, current treatments have severe side effects including depression, weakness, flu like symptoms, aches, coughs and itching. Reduced side effects in addition to the psychological benefits from an oral treatment will be of great importance to individuals. Ease of application and reduced effects on daily life with less need of support from others will be a significant improvement for people taking the treatment. The course of treatment down to 12 weeks from 24-48 weeks is a notable advancement and is likely to result in improved treatment fidelity and completion rates.	describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	The Hepatitis C Trust	The ability to remove interferon from the treatment regime, to which Sofosbuvir will contribute, is indeed a 'step-change'. The long-term effects of interferon on quality of life after treatment cessation have never been properly studied but at least 2 reports suggest it is an issue (Post Treatment Survey Report 2010 and Recovery from hepatitis C treatments 2009 available in resources/reports on our website – www.hepctrust.org.uk). Interferon-free (and possibly interferon-sparing) regimes may therefore bring so far unquantified benefits.	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	Royal College of Nursing	Yes. Without interferon for some this may allow the treatment active drug using populations and in doing so could lead to a significant reduction in the infection of others in the future. It has potential to allow access for those with significant co-morbid conditions and more difficult to cure with current available therapies	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.
	UK Clinical Pharmacy Association	Yes.	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will

Section	Consultees	Comments	Action
			consider this information during the course of the appraisal. No changes required.
Other considerations	Gilead Sciences	**HIV co-infection** Gilead will have clinical data on HIV co-infection across GT1, GT2 and GT3 that could be used to inform this HTA.	Comment noted. HIV co-infection is currently listed as a subgroup under other considerations in the scope. The Committee will consider this subgroup if the evidence allows. No changes required.
		Response to previous treatment Gilead will have information to allow this subgrouping to occur.	Comment noted. Response to previous treatment is currently listed as a subgroup under other considerations in the scope, which the Committee will consider if the evidence allows. No changes required.
		Presence or absence of IL28b polymorhphism This is not a relevant subgroup as there are no major differences observed in relation to SOF efficacy for this subgroup. Indeed it should be noted that classical markers such as RVR (rapid virologic response), non-response, BMI (body mass index) or IL28B do not provide predictable markers for treatment success / failure with SOF.	Comments noted. The attendees at the scoping workshop discussed the proposed IL28 polymorphism subgroup and agreed that as the test is not used routinely in clinical practice this was not relevant to the scope. The scope has been updated accordingly.
	Royal College of Pathologists	None.	Comments noted. No changes required.
	Terrence Higgins Trust	Completion of treatment and treatment retention should also be considered. With current treatment regimes expanding between 24-48	Comments noted. The issue of adherence to treatment was raised

Section	Consultees	Comments	Action
		weeks, with severe side effects, treatment fidelity should also be considered. Incomplete treatment evidently incurs costs for the NHS without the benefit of effective treatment. Therefore improved completion rates overall should also be considered.	at the scoping workshop. The attendees understood that adherence was not a particular concern for these patients and therefore adherence to treatment was not considered to be a relevant outcome. No changes required.
	The Hepatitis C Trust	We believe it would be useful to consider the presence or absence of cirrhosis. We do not consider the IL28B polymorphism to be relevant.	Comments noted and raised at the scoping workshop. Attendees at the scoping workshop agreed that IL28 polymorphism subgroup analyses were not relevant and should not be included in the scope. Attendees acknowledged that subgroup analyses (such as presence or absence of cirrhosis) will be provided at the manufacturer's discretion if the evidence allows.
	Southampton Health Technology Assessments Centre (SHTAC)	Will low/high baseline viral load be considered as a subgroup?	Comment noted and raised at the scoping workshop. It was recognised by attendees that this subgroup was relevant for the comparators, but not for considering the efficacy of sofosbuvir. Attendees at the workshop agreed this should not be included as a subgroup. No changes required.
	Merck Sharp & Dohme (MSD)	Have the most appropriate comparators for sofosbuvir for treating hepatitis C been included in the scope? Are the comparators listed routinely used in	Comments noted. No changes required.

Section	Consultees	Comments	Action
		clinical practice? There is wide acceptance that boceprevir is considered the standard of care of genotype 1 patients with chronic hepatitis C who are treatment naïve or have been previously treated, therefore boceprevir is an appropriate comparator for the genotype 1 population. MSD would like to highlight the lack of controlled clinical trials in the genotype 1 population, therefore only a naïve unadjusted comparison against boceprevir, telaprevir or peginterferon/ribavirin is possible. As a result of this, NICE will have difficulty in making any robust conclusions about the relative efficacy and cost-effectiveness of sofosbuvir compared to the existing NICE-recommended treatment options for genotype one patients.	
	UK Clinical Pharmacy Association	Comparison with telaprevir & boceprevir. Use in patients who cannot tolerate interferon – even if treatment is less effective than using interferon it may be better than nothing.	Comments noted. No changes required.
	Janssen	Janssen suggests that if evidence allows: • The patient groups should be split by level of fibrosis.	Comments noted and raised at the scoping workshop. Attendees at the workshop agreed that the level of fibrosis should not be considered as a subgroup. No changes required.
Questions for consultation	Gilead Sciences	SOF represents a breakthrough treatment for HCV, offering: • Superior clinical efficacy vs. NICE-recommended SoC (even amongst cirrhotic patients who are typically the most difficult to treat) • A side effect profile similar to placebo and superior to the current SoC • Shorter treatment duration (from 24-48 weeks down to 12 weeks) with the opportunity for an IFN-free, all-oral treatment regime for GT2 and GT3 (this is particularly important for those patients	Comments noted. The manufacturer is encouraged to describe the innovative nature of sofosbuvir its evidence submission. The Committee will consider this information during the course of the appraisal. No changes required.

Section	Consultees	Comments	Action
		unsuitable for IFN) The implications are as follows: • Significantly greater proportion of HCV patients can achieve a cure • Decreased treatment-emergent side effects and discontinuations compared to NICE-approved SoC – leading to decreased healthcare costs associated with managing the potentially severe side effects • Improved QoL for patients as demonstrated by a reduced treatment side effect profile and decreased duration of treatment • As this is an infectious disease with the potential for cure, by improving cure rates together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden to the NHS of HCV All of this means that there is an urgent need for timely patient access to SOF, re-iterating the need for timely NICE review and guidance. Given the urgent need for those patients with life-threatening liver disease and no treatment options, Gilead Sciences Ltd. wishes to ensure that the timing of NICE guidance aligns with the accelerated regulatory review timelines for SOF. We therefore strongly support an STA submission in 2013 to support this alignment.	
	Terrence Higgins Trust	We would encourage the committee to prioritise the appraisal and ensure that it proceeds as soon as possible. With the potential to improve thousands of lives we would not wish to see the appraisal incur unnecessary delays due to forthcoming changes to technology appraisals.	Comments noted. No changes required.
Additional comments on the draft scope.	Foundation for Liver Research	Already at this stage the cost of this agent and other new oral drugs that will shortly follow, will be high. QALY calculations are likely to be in favour.	Comments noted. No changes required.
	Children's HIV Association (CHIVA)	Children are understandably not being considered within the remit of this consultation. A statement from this TA that sofosbuvir needs evaluating in the paediatric population within the framework of well-designed multicentre network studies would be welcomed.	Comment noted. No changes required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
British Association for the Study of the Liver Nurses Forum
Healthcare Improvement Scotland
Medicines and Healthcare products Regulatory Agency

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir for treating chronic hepatitis C

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add Addaction	NICE secretariat		Not added	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Addaction has not been added to the matrix of consultees and commentators.

2.	Add Alliance	NICE secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Alliance has been added to the matrix of consultees and commentators under 'patient groups'
3.	Remove Chinese National Healthy Living	NICE secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Chinese National Healthy Living has been removed from matrix of consultees and commentators.
4.	Add Drugs Action	NICE secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Drugs Action has been added to the matrix of consultees and commentators under 'patient groups'

5.	Remove Independent Age	NICE secretariat		Removed	Independent Age have been removed from the matrix at their own request.
6.	Remove Release	NICE secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Release has been removed from the matrix of consultees and commentators.
7.	Remove British Association for Services to the Elderly	NICE secretariat		Removed	This organisation has disbanded.
8.	Remove British Transplantation Society	NICE secretariat		Removed	British Transplantation Society have been removed from the matrix at their own request.
9.	Add HCV Action	Hepatitis C Trust		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. HCV Action has been added to the matrix of consultees and commentators under 'patient groups'

10.	Re-classify Public Health England	NICE secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group - commentator'.
11.	Re-classify Public Health Wales NHS Trust	NICE secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group - commentator'.