NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Sofosbuvir for treating chronic hepatitis C

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Gilead	Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We recognise the complexity of this appraisal and have welcomed both the engagement of NICE and the Appraisal Committee throughout the process in accepting and considering relevant data. We have also appreciated the opportunity to respond to comments during the Appraisal Committee meetings and feel that this has helped address areas of uncertainty and enabled the Committee to release these provisional recommendations for consultation. We have provided comments below in response to the specific consultation questions. In addition points of clarification and factual inaccuracies relating to specific sections of the ACD are provided in the following table. • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We welcome the provisional recommendations that sofosbuvir should be made available for the majority of adult patients with chronic hepatitis C and are pleased that the Committee has recognised the significant unmet need for genotype (GT) 1 treatment experienced patients. We are disappointed that the Committee was unable to give a positive provisional recommendation for people with GT4 and ask the Committee to re-consider their current recommendation for this patient group as GT4 HCV is an area of significant unmet need. Whilst HCV genotype 4 (GT4) only accounts for 5% of all HCV genotypes in the UK, the prevalence of GT4 in the UK is increasing due to migration, HIV/HCV co-infection and intravenous drug use. GT4 HCV is also typically less responsive to interferon/ribavirin based therapy and the currently NICE-approved oral direct acting agents (DAAs - telaprevir and boceprevir) are not indicated for this patient subgroup. We appreciate the Committee's concern that the evidence base for GT4 is limited but would highlight that sofosbuvir (in combination with peginterferon alfa and ribavirin for 12 weeks) is the only direct acting HCV antiviral agent to have been studied in this population in Phase 3 trials to date. In the Phase 3 study NEUTRINO treatment with sofosbuvir resulted in high rates of SVR12 in GT4 patients (sub-group analysis: 27/28 patients; 96%). • In addition, this ICER whilst considered conservative (since the SVR for cirrhotic patients [50%] is based on only 2 patients), demonstrates that sofosbuvir is cost-effective in patients with GT4-6 HCV with an ICER falling within the £20,000 to £30,000 range. This ICER would also likely become lower in the event benefits such as relief of cognitive ability and public health benefits	Comment noted. The Committee took into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, and concluded that sofosbuvir plus peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 HCV who have cirrhosis could be considered a cost-effective use of NHS resources. The Committee considered that it was plausible that the ICER in genotypes 4, 5 or 6 HCV with cirrhosis could also be within the range that is normally accepted as being cost

Consultee	Comment	Response
	were taken into account, a factor recognised in the ACD (Section 4.39).	effective, that is between £20,000 and £30,000 per QALY gained (see FAD sections 4.35 and 4.36).
	• **Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence** Yes, whilst recognising the complexity of this appraisal we believe these are reasonable interpretations. We have provided comments on areas which would benefit from additional clarification and factual inaccuracies in the attached table.	Comment noted.
	• **Has all of the relevant evidence been taken into account?** Whilst we can confirm that all relevant clinical trial evidence has been taken into account we are disappointed that despite the available evidence the Committee felt unable to provide a positive recommendation for the use of sofosbuvir in GT4 HCV patients despite the evidence that sofosbuvir is both clinically and cost-effective in this group. Further details are provided above.	Comment noted.
	• **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No and we support the statements in the ACD (Sections 4.11 and 4.38) that any recommendations on the use of sofosbuvir do not exclude patients with present or previous drug use (Section 4.38) or HCV/HIV co-infected patients (Sections 4.11).	Comment noted. Following consideration of comments received during the consultation on a decision to amend the deferred funding, the Guidance Executive decided that an extension to the normal period was required. See Section 5 of the FAD.
	• **Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply:** • **The health technology cannot be appropriately administered until training is in place?** • **The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?** • **The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?** There are no reasons for an extension to be given for relevant health bodies to provide funding to ensure sofosbuvir is available within three months of the final guidance being published by NICE. No training is	

Consultee	Comment	Response
	required to administer sofosbuvir and there is no requirement for any additional infrastructure or resources to be put in place. Given the clear and significant unmet need for patients who would benefit from access to this new technology we feel it is imperative that this guidance is published without delay. We look forward to the final recommendations and respectfully request that the Committee considers expanding the provisional recommendations to include the use of sofosbuvir in GT4 HCV patients.	Comment noted. During consultation the Institute received varied responses on whether it was possible to implement the guidance within 3 months and noted that changes to the timescale for implementation would need to be agreed by NHS England and the Secretary of State. (see section 4.44 of the FAD)
British Society of Gastroenterology	The British Society of Gastroenterology (BSG) welcomes the latest revisions but is concerned that genotype 4,5 and 6 pts have been denied access when the data for this group is as strong as that for other groups that are included. For the remaining genotypes, this evaluation appears, a sensible and appropriate approach to the use of Sofosbuvir given the experience and published data. Patients infected with the two major genotypes, 1 and 3, will be able to access Sofosbuvir where appropriate, and specifically where the results of conventional PEG-interferon plus Ribavirin can be improved upon: • The excellent outcome of G1 naives with 12/52 PEG-Interferon/Ribavirin/Sofosbuvir will deliver cure to most recipients with a reduced period of interferon exposure. • Non-cirrhotic genotype 3 naives will continue to receive PEG/Ribavirin in the clinic, whereas treatment exposed and/or cirrhotic 3's will have Sofosbuvir added unless they are Interferon intolerant, when they will just receive Sofosbuvir and ribavirin. • Treatment experienced genotype 1's will also be eligible. Genotype2 patients rarely fail short-course PEG/Ribavirin therapy and this will remain the mainstay of treatment. However those unable to tolerate PEG and the tiny number of treatment failures can access Sofosbuvir with Ribavirin. HIV co-infected and liver transplant patients, whilst small in number, represents a considerable challenge to conventional hep c therapy. Drug-drug interactions, frailty of liver and side-effects reduces acceptability and success of PEG based therapy. Access to Sofosbuvir for this group is a rational decision. Reviewing the data and submission for genotype 4, 5 & 6, minority subtypes in UK, it does appear that there is some inconsistency in the recommendations. The Neutrino study (page 8 and 9) of treatment naïve patients included 28 G4's, a single G5 and 6 G6's. An SVR was seen in 27/28 G4, and all G5 and G6's. In addition the Gilead ICER calculation is below the NICE threshold. Sofosbuvir would therefore appear cost-effective for these rare genotypes. Thus, genotype 4, 5 and 6 patients, logically, should be	Comment noted. The Committee took into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, and concluded that sofosbuvir plus peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 HCV who have cirrhosis could be considered a cost-effective use of NHS resources. The Committee considered that it was plausible that the ICER in genotypes 4, 5 or 6 HCV with cirrhosis could also be within the range that is normally accepted as being cost effective, that is between £20,000 and £30,000 per QALY gained (see FAD sections 4.35 and 4.36).

Consultee	Comment	Response
	allowed access to Sofosbuvir. In conclusion, the BSG would be broadly supportive of this evaluation. However, the BSG would advocate strongly for patients with genotypes 4,5 and 6 also being allowed access to Sofosbuvir. Exclusion of this small, but important group of patients disregards the limited, but indubitable evidence and detracts from what is otherwise a balanced and apposite judgment.	
Hepatitis C Trust	The Hepatitis C Trust would like to express its disappointment that NICE is minded not to recommend Sofosbuvir for any patients with genotype 4, 5 or 6. These patients will therefore have no access to any drugs other than peg-interferon and ribavirin, despite the fact that the sub-group analysis of NEUTRINO should a 96% SVR12. There are a significant number of patients who would look at 96% SVR with less interferon and consider that a good trade-off who would not do just peg-interferon and ribavirin with maybe a 60-70% chance of SVR (and whose comparator is therefore no treatment, greatly lowering the ICER). One of the issues is of course the small numbers of genotype 4, 5 or 6 in the relevant trials, so that for example a single non-SVR cirrhotic can have a significant impact on ICERs, and the small numbers also make the ICERs more uncertain. The reason for the small numbers in the trials is that these are comparatively rare genotypes in the developed world, where trials typically are held. This applies equally to the UK where only some 5% of people living with hepatitis C have genotypes 4, 5 or 6. We feel that in some sense the small numbers result in discrimination and we do not think it should count against them. Indeed, we would argue that, if the genotypes were combined in proportion to their prevalence and genotypes 1, 4, 5 and 6 considered as a combined group, Sofosbuvir would be cost effective for the group as a whole. We therefore request that NICE reassess these genotypes.	Comment noted. The Committee took into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, and concluded that sofosbuvir plus peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 HCV who have cirrhosis could be considered a cost-effective use of NHS resources. The Committee considered that it was plausible that the ICER in genotypes 4, 5 or 6 HCV with cirrhosis could also be within the range that is normally accepted as being cost effective, that is between £20,000 and £30,000 per QALY gained (see FAD sections 4.35 and 4.36).
	We also feel that the ICERs across the board are almost certainly too high. As we continue to note, the cost of transmission prevention as a result of successful treatment cannot logically continue to be excluded from calculations for infectious diseases such as hepatitis C. Furthermore, much of the evidence used for disease state transition is old and, in our view out of date. Early estimates of the likelihood of progression to cirrhosis may be too conservative, as we see larger cohorts with infection of more than 30 years. Equally we do not believe that quality of life estimates have properly taken into	Comments noted. The Committee agreed with the clinical experts and patient experts that there were other benefits to patients (such as relief of loss of cognitive ability

Consultee	Comment	Response
	account either the debilitating consequences of interferon treatment that for some people persist *after* treatment has ended for some years or the positive impact of treatment on people with co-morbidities such as haemophilia or cryoglobulinaemia.	in people with HCV) and public health benefits (such as reduced transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, would decrease the ICERs (see FAD section 4.42). The company used transition probabilities for disease progression from 2 published UK health technology assessments and 1 UK study: Hartwell et al. (2011), Shepherd et al. (2007), and Grishchenko et al. (2009), which used estimates from the Trent database (see FAD section 3.32).
NHS England	**NHS England Response to NICE ACD – Sofosbuvir for treating chronic hepatitis C (ID654)** NHS England would like to provide the following response to the ACD – Sofosbuvir for treating chronic hepatitis C. NHS England is generally supportive of the recommendations contained within the ACD. Whilst we recognise some of the limitations of the RCTs performed in some genotypes we also recognise that sofosbuvir within the recommendations falls well within the accepted QALY threshold. We would like to raise the following points for consideration by NICE: 1. The wording in a number of the conclusions is that 'sofosbuvir is recommended <u>*as an option*</u> for…' but it is essential that treatment decisions are made by clinicians experienced in the management of hepatitis C (preferably working as a team through MDT meetings), to ensure that the most appropriate and cost effective treatments are used. **NHS England would expect that this is included in the recommendations.** 2. The criteria relating to sofosbuvir with ribivirin needs to be more explicit. Given the cost of such treatment could be circa £70k per patient course we are concerned that the definition of *'interferon unsuitable – includes people who are intolerant to and ineligible for interferon'* could lead to wide interpretation and would lead to overuse of this combination. This regimen should clearly be seen as a second line therapy, for patients who are truly unable to take interferon. **NHS England would expect the criteria to be changed to exclude naïve patients unless they have**	Comment noted. In section 4.4 of the FAD, the Committee agrees with comments received during consultation that treatment should be focused in specialist centres and that treatment decisions should be made preferably by a multidisciplinary team. This information is not typically included in the recommendations made by the Committee. Comment noted. The Committee considered the use of sofosbuvir and ribavirin in people for whom peginterferon was unsuitable. They heard from the company that that

Consultee	Comment	Response
	a specific contraindication to pegylated interferon and that there is further refinement of the definition of 'interferon unsuitable'. 3. We note that Genotype 2 is not mentioned at all in the summary of treatment recommendations for sofosbuvir/pegylated interferon/ribavirin. Whilst we appreciate that evidence is limited in this group, for completeness there should be some statement as to whether or not NICE recommends this treatment as an option in Genotype 2. **NHS England asks that a statement as to the suitability of sofosbuvir for Genotype 2 is included in the recommendations.**	sofosbuvir and ribavirin should would be regarded as a second-line option in people in urgent need of care with genotype 1, 4, 5, or 6 HCV in whom peginterferon was contraindicated (as described in the summary of product characteristics) or people whose disease did not have an adequate response to treatment with peginterferon See section 4.41 of FAD
	4. NHS England would like to seek a waiver to the period within which NICE TA's are funded (ie within 3 months). The first reason for the request for an extension relates partly to the capacity of the NHS to meet what is expected to be an increased demand for drugs such as sofosbuvir. In other words, NHS England believes that the health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place. This includes the ability to monitor the results of treatment ie recording and reporting of a sustained virological response rate. The second reason is because at the prices proposed by the manufacturer in their NICE submission, this technology is not affordable at the quantum of new expenditure it would represent (particularly if the backlog of prevalent cases become immediately eligible for funding alongside incidence cases). The third reason is because further therapies for Hepatitis C are likely to become available in the foreseeable future, and the NHS would wish to see their comparative cost effectiveness assessed before selecting one particular option for hundreds of millions of pounds of new public investment. **NHS England formerly requests a waiver or substantial extension over several years to the normal implementation period for the reasons given above.**	Comment noted. Sofosbuvir plus peginterferon alfa and ribavirin does not have a license for the treatment of people with genotype 2 HCV. This is reflected in the summary table of recommendations in the FAD (table 1). Comment noted. (see section 4.45 and 5.1 of the FAD) Following consideration of comments received during the consultation on a decision to amend the deferred funding, the Guidance Executive decided that an extension to the normal period was required. See Section 5 of the FAD.
Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above ACD2. Overall, our experts are far more supportive of the new version. They feel that there has been considerable reappraisal and that the recommendations are in the main clear and reasonable; addressing a significant unmet need. However,	

Consultee	Comment	Response
	we would like to make the following points:	
	• The wording in a number of the conclusions that 'sofosbuvir is recommended as an option for…' allows for considerable clinical variation in the actual treatment used for specific patient groups. It is essential that treatment decisions are made by clinicians experienced in the management of hepatitis C (preferably working as a team through MDT meetings) to ensure that the most appropriate and cost effective treatments are used.	Comment noted. In section 4.4 of the FAD, the Committee agrees with comments received during consultation that treatment for chronic hepatitis C with sofosbuvir and ribavirin with or without peginterferon should be focused in specialist centres and that treatment decisions should be made preferably by a multidisciplinary team.
	• This is particularly the case for interferon-free regimens (ie sofosbuvir plus ribavirin), which may be seen as a safer and easier option (and may be preferred by many patients). There is concern that inexperienced clinicians, who may not consider using interferon because of adverse effects and monitoring requirements, might choose to start treating patients with sofosbuvir/ribavirin. The current criterion for using interferon free treatment ('ineligibility or intolerance') is vague, and open to misinterpretation or misuse which could pose a risk to some patients. It should therefore be clarified within the guidance. This regimen should clearly be seen as a second line therapy, for patients who are truly unable to take interferon. • Genotype 2 is not mentioned at all in the summary of treatment recommendation for sofosbuvir/interferon. Our experts appreciate that evidence is limited in this group, but for completeness there should be some statement as to whether or not NICE recommends this treatment as an option in g2.	The Committee took into consideration the place of sofosbuvir in dual therapy (interferon-free regimens) compared with triple therapy. They heard from the manufacturer that dual therapy was only licensed in people in urgent need of care with genotype 1, 4, 5, or 6 HCV in whom interferon was contraindicated (as described in the summary of product characteristics) or people whose disease did not have an adequate response to interferon based treatment. (see section 4.41 of the FAD)
	• While it is appreciated that the number of patients studied with genotypes 4, 5, and 6 is small, there is more evidence for genotype 4 than the other two, and they should not necessarily be lumped together. There is a real unmet need for treatment for patients with g4 who have not responded to currently available therapies, and we would welcome a reappraisal of the evidence specifically in this group (although our experts recognise that the evidence submitted may not be adequate for the minimum requirements of NICE).	Comment noted. Comment noted. Sofosbuvir plus peginterferon alfa and ribavirin does not have a license for the treatment of people with

Consultee	Comment	Response
		genotype 2 HCV. This is reflected in the summary table of recommendations in section 1.1 of the FAD.
	• Genotype 4 accounts for up to 30% of the UK HIV/HCV co-infected population (UK CHIC study - unpublished data) and represent a significant unmet need in terms of liver disease burden and risk of progression. Our experts would therefore urge reconsideration of allowing Sofosbuvir treatment for the IFN-eligible G4 sub-group with advanced fibrosis.	Comment noted. The Committee has recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD section 1.1).
	• In para 4.19 it is stated that generic (Teva) ribavirin is licensed for use with pegylated interferon alpha 2b. The licence (and recommendation from EMA/MHRA) states that Teva ribavirin is for use with interferon alpha 2b (not pegylated). While our understanding is that bioequivalence studies support the use of this generic preparation, it is important (given that NICE is basing its cost efficacy calculations on the use of the Teva drug) to confirm that NICE recommends the use of generic ribavirin with all types of interferon, and with sofosbuvir.	Comment noted. The Committee has noted that the summary of product characteristics states that people with HCV and HIV co-infection should have the same sofosbuvir treatment schedule as people with HCV mono-infection, and concluded that this was appropriate. People with HIV should be offered treatment in line with the recommendations made by the Committee which includes triple therapy in people with genotype 4,5 or 6 HCV who have cirrhosis) Comment noted. In response to consultation the company included the generic cost of ribavirin in its revised base-case analysis, but noted that the Medicines and Healthcare products Regulatory Agency

Consultee	Comment	Response
		stated that generic ribavirin should only be used in combination with interferon alfa-2b, which only has 3% of the market share in the UK. The Committee concluded that the generic cost of ribavirin had a small effect on the ICER as demonstrated by the ERG analysis (see FAD section 4.19).

Comments received from commentators

Commentator	Comment	Response
Janssen	We are concerned that the cost effectiveness of sofosbuvir plus peginterferon/ribavirin (PR) versus telaprevir+PR in this subpopulation (genotype 1 HCV) is biased against telaprevir for the following reasons: 1. There has been no examination of the impact of a downward adjustment of the SVR12 for sofosbuvir+PR estimated for the non-cirrhotic subgroup to account for reduced efficacy in a cirrhotic subgroup. As noted in the ACD, and reflected in the SVRs applied in the manufacturer's analysis for the comparator treatments, patients with cirrhosis have a poorer SVR. Yet the manufacturer's analysis assumes 78% SVR12 regardless of cirrhosis status, compared to 70.6% and 47.2% SVR for telaprevir-treated non-cirrhotic and cirrhotic patients, respectively. 2. There has been no analysis of the impact of up to a 24 week treatment duration for sofosbuvir+PR which, in line with the Summary of Product Characteristics (SmPC), should be considered for patients with cirrhosis and/or prior null response to PR. Conversely, response guided treatment is incorporated to the telaprevir arm by applying an average treatment duration of 39.0 weeks. We note that this average treatment duration is entirely inconsistent with the telaprevir SmPC and the cited NICE STA; the latter reporting 10.7 week telaprevir treatment duration for treatment-experienced patients. 3. There has been no assessment of the impact of varying the distribution of prior relapsers, partial responders and null responders used to inform the pooled SVR estimate for telaprevir+PR. Whilst sofosbuvir+PR effectiveness amongst these previously-treated subgroups is unknown,	Comment noted. The company provided stratified ICERs for the population of genotype 1 HCV without cirrhosis and with cirrhosis using the sustained virological response rates for sofosbuvir from NEUTRINO in the model and the sustained virological response rates from the telaprevir STA. The Committee noted that the company did not model the impact of extending the duration of sofosbuvir plus peginterferon alfa and ribavirin for people with one or more factors which are historically associated with lower response rates to interferon therapies. The company did not present an economic analysis varying the prior treatment response of patients receiving telaprevir.

Commentator	Comment	Response
	and therefore presumably assumed equal, the distribution used in the manufacturer's basecase will determine the SVR for comparators.	The company used the sustained virological response rates from the previous telaprevir STA to inform its model.

Comments received from members of the public

Role*	Comment	Response
NHS Professional	I think that the document as a whole is a massive leap toward the beginning of the eradication of hepatitis C which has been a long time coming - it is positive about the new advances in this field and acknowledges that we need to be able to treat as many people as possible effectively and with the least amount of time, including potential time from work, with a greatly improved side effect profile.	Comment noted.
	I would like to make a couple of other points however: I treat patients with genotype 4/5/6 on a frequent basis, due to local demographic (including those who are co-infected with HIV and these genotypes) and, bearing in mind that the clinical trials show much improved efficacy with these types of HCV, it is disappointing that I will have to continue to use 48 weeks of Peg/Ribavirin with these genotypes.	Comment noted. The Committee has now recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD section 1.1).
	I would also like to be able to ready patients to start treatment as soon as possible on the new regimes, so is there any way the lead times for starting patients on treatment could be cut?	Comment noted(see section 4.45 and 5.1 of the FAD)
	Many thanks	Following consideration of comments received during the consultation on a decision to amend the deferred funding, the Guidance Executive decided that an extension to the normal period was

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Comment	Response
		required. See Section 5 of the FAD.
NHS Professional	I am surprised at the committees decision to exclude patients with genotype 3 who are treatment Naive and non-cirrhotic. It is difficult to see how having to have failed treatment with PEG Ribavirin (about 45% of patients) before being allowed Sofosbuvir can be cost effective or clinically sound. Given the absence of alternative agents with good activity against genotype 3 (most of the new DAAs are for genotype 1) this greats a really poorly served and quite large patient group at a time when most patients with HCV should be anticipating a swift cure.	Comment noted. The Committee noted that when stratified by cirrhosis status, the ICER for people with treatment-naive genotype 3 HCV without cirrhosis who are eligible for treatment with interferon was approximately £40,600 per QALY gained, whereas the ICER for people with cirrhosis was approximately £6600 per QALY gained. The Committee noted that the effect of using the combined cohort analysis which includes a larger subgroup without cirrhosis and a small subgroup with cirrhosis, resulted in a combined cohort ICER that was artificially low (£21,900 per QALY gained). The Committee considered that despite this uncertainty there was more confidence around the ICER for the subgroup with cirrhosis because treatment remained cost effective despite using a variety of assumptions including those suggested by the ERG in its exploratory analyses. The Committee also acknowledged that people with cirrhosis are in greater need of treatment than those without cirrhosis.
NHS	1.4 Sofosbuvir, in combination with peginterferon alfa and ribavirin, is not recommended for treating	Comment noted. The

Role*	Comment	Response
Professional	genotype 4, 5 and 6 chronic hepatitis C in adults. This recommendation will further widen the health inequality gap between the white population and the ethnic minorities who are mainly infected with genotype 4 in the UK. Combination therapy (pegylated interferon and ribavirin) has never been effective in eradicating the HCV virus in these communities from trial data and clinical observations . There is an opportunity to cure those ethnic minorities infected with HCV (genotype 4) and reduce the burden of disease and improve quality of life and ICER seems to determine who should be given treatment and have a chance of a cure and who should be sentence to death. Are their lives not worth saving? Where is your duty of care or your utilitarian stance? I am aware you have a duty to abide by guidance in spite of the serious consequences of your actions, however, be the change and not let the Government cost effective guidance destroy lives of some of the most vulnerable groups in our society. Why not recommended the following Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended for treating genotype 4, 5 and 6 chronic hepatitis C in adults, only if they had treatment for hepatitis C before Sofosbuvir, in combination with peginterferon and ribavirin, is recommended as an option for treating genotype 4, 5, 6 chronic hepatitis C in treatment naive adults with cirrhosis.	Committee considered the impact of potential equality issues on the ACD and further explored the prevalence of people from different family origins for each genotype. The Committee considered additional information provided by the company using a revised economic model on the cost effectiveness of sofosbuvir in genotypes 4, 5 and 6. The Committee has now recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD sections 1.1 and 4.34-8).
Patient organisation	I would just like to underline how appropriate I feel it is that NICE has reflected on the evidence of the effectiveness of sofosbuvir in people co-infected with HIV. I feel this second draft guidance is much more equitable, reflects the science as well as recommendations in the European Association for the Study of the Liver Treatment Guidelines that co-infected people should not be treated any differently to mono-infected people. Thank you for this making this huge step towards access to improved hepatitis therapy for people with HIV.	Comment noted.
Patient organisation	We thank NICE for its considered assessment of the cost effectiveness of sofosbuvir, and for noting and acting on the consultations received after the promulgation of the first appraisal. The revised NICE appraisal offers the opportunity to achieve high rates of cure after treatment for patients with genotype 1, 2 and 3. However we believe that patients with genotype 4 also merit treatment with sofosbuvir. The in-vitro data indicates that sofosbuvir is active against genotype 4. Although the clinical trial data is limited, the available data confirms that sofosbuvir, PEG IFN and RBV is highly efficacious against genotype 4. The British Association for the Study of the Liver and the British Viral Hepatitis Group would like to highlight that genotype 4 is found in minority populations in the UK, and that the inability to offer sofosbuvir to patients with genotype 4 may risk challenges via equality policies. Patients with genotype 4 who have not responded to PEG IFN and RBV presently have no other options for treatment. The ICERS for sofosbuvir,	Comment noted. The Committee considered the impact of potential equality issues on the ACD and further explored the prevalence of people from different family origins for each genotype. The Committee considered additional information provided by the company using a

Role*	Comment	Response
	PEG IFN and RBV suggest that a 12 week regimen is cost effective within a £30,000 per QALY ceiling. Relatively few patients are chronically infected genotype 4. Thus, for these reasons, we would ask NICE to consider including the approval of a 12 week regimen of sofosbuvir, PEG IFN and RBV for naive patients and prior non-responders who are tolerant of IFN.	revised economic model on the cost effectiveness of sofosbuvir in genotypes 4, 5 and 6. The Committee has now recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD sections 1.1 and 4.34-8).
NHS Professional	Many thanks for the opportunity to comment on this second appraisal document. I was very encouraged to see that NICE has decided to modify the earlier decision to not recommend Sofosbuvir for Genotype 3 HCV and that it now recognises the unmet need in this population. Similarly, I fully agree with the decision not to recommend the use of the drug for patients with Genotype 5 and 6 as I do not think there is sufficient data to recommend this. However, I am concerned that patients with Genotype 4 will not have access to the drug as currently stands. Patients with Genotype 4 represent 5% of the population of HCV patients in the UK. There are, therefore, substantial numbers of patients who would benefit from Sofosbuvir. These patients mostly come from specific ethnic backgrounds; indeed Egyptian patients are mostly G4. Whilst I recognise that the manufacturer did not submit data for more than 28 patients in the original submission, data that has been presented since includes significantly more numbers. Rune et al presented data at the European Association for the Study of Liver Disease in London in April 2014 showing SVR rates of 100% and 87% respectively in 14 treatment naive and 15 treatment experience patients treated with 24 weeks of Sofosbuvir and Repairing only. The equivalent figures with 12 weeks of the same regimen were 79% and 59% respectively in 14 treatment naive and 17 treatment experienced patients. This data represents good efficacy in 60 patients with G4 and is comparable and probably superior to the 40-50% historical success rates with PEG-IFN and repairing. There is also a study from Egypt that will be presented at the AASLD meeting in November 2014 with 100 patients showing significantly better efficacy of Sofosbuvir containing regimens (personal communication). Only this week I saw a genotype 4 cirrhotic 65 year old lady who had failed dual therapy and also had failed a simeprevir containing triple therapy regimen for 4 weeks. Without access to Sofosbuvir I have nothing to offer her to prevent the inevitable progression of her liver disease.	Committee considered the impact of potential equality issues on the ACD and further explored the prevalence of people from different family origins for each genotype. The Committee considered additional information provided by the company using a revised economic model on the cost effectiveness of sofosbuvir in genotypes 4, 5 and 6. The Committee has now recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD sections 1.1 and 4.34-8)

Role*	Comment	Response
	With the data above in mind, I would urge the committee to review the recommendation for treatment of G4 patients with Sofosbuvir as this drug would be an important addition to our armamentarium for the treatment of G4 patients; whose options are currently very limited.	
NHS Professional	BHIVA and BASHH would like to thank the NICE Appraisal Committee for considering HIV/HCV co-infected patients in this appraisal and for agreeing that responses in co-infected patients are no different to those seen in mono-infected patients.	Comment noted.
NHS Professional	BHIVA and BASHH agree with the NICE Appraisal Committee that manufacturers and the Evidence Review Group (ERG) need to show a separate cost-effective analysis for co-infected for future single technology appraisals, taking into account the high rates of progression of liver disease and normal life-expectancies of HIV patients successfully treated with antiretroviral therapy.	Comment noted. In section 4.40 of the FAD, the Committee has expressed legitimate concerns about the modelling for the HIV and HCV co-infected group, and has emphasised that future economic analyses should be presented separately for this population.
NHS Professional	'Genotype 4 accounts for up to 30% of the UK HIV/HCV co-infected population (UK CHIC study - unpublished data) and represent a significant unmet need in terms of liver disease burden and risk of progression. Both BHIVA and BASHH would urge reconsideration of allowing Sofosbuvir treatment for the IFN-eligible G4 sub-group with advanced fibrosis.	Comment noted. The Committee has recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD section 1.1).
Patient	I have read, with interest, the Draft Guidance, together with all paperwork published by NICE in relation to the Draft Guidance. I note that despite accepting Sofosbuvir's clinical efficacy in treating, and in all likelihood curing, HCV where the patient has Genotype 4, 5 or 6, the Draft Guidance suggests that NICE is not currently minded to recommend that Sofosbuvir be prescribed to HCV sufferers with Genotypes 4, 5, or 6. That decision is based purely on QALY assessments for those Genotypes. NICE's current thinking in relation to Genotypes 4, 5 and 6 is out of sync with the advice published by the Scottish Medicines Consortium which has recommended Sofosbuvir be prescribed to all HCV Sufferers, including those with Genotypes 4, 5, or 6. It is also out of sync with the decisions taken by other equivalent bodies across Europe and North America.	Comment noted. The Committee has recommended sofosbuvir, in combination with peginterferon alfa and ribavirin, as an option for treating genotype 4, 5 or 6 chronic hepatitis C in adults with cirrhosis only (see FAD section 1.1).

Role*	Comment	Response
	I also note that stakeholders from neither the Haemophilia nor the Contaminated Blood Product communities were consulted by NICE as part of NICE's evaluations of Sofosbuvir. Whatever the background to this lack of consultation (a failure by NICE to consult, or a failure by representative bodies for those communities to participate), such lack of consultation has, I would suggest, led to **Draft Guidance which, at present:** **(a) fails to correctly assess the QALY for HCV sufferers who are Haemophiliacs;** **(b) fails to take into account other health related benefits which would flow from recommending that Sofosbuvir be made available to treat HCV sufferers who are Haemophiliacs; and** **(c) inadvertently places a significantly greater cost burden, outweighing the cost of Sofosbuvir by a multiple, on limited NHS resources where HCV sufferers who are Haemophiliacs require a consequential procedures or surgery as a result of the HCV going uncured.** **From a wider "cost to the NHS perspective", given that the clinical efficacy of Sofosbuvir for Genotypes 4, 5 and 6 is accepted by NICE, the current Draft Guidance also:** **(d) potentially opens up the NHS to wide-ranging and expensive litigation from HCV sufferers where the infection was caused by NHS contaminated blood products (given the higher incidence of Genotypes 4, 5 and 6 sufferers within that community) and they can establish that NHS negligence caused the infection, compounded by the fact that some may now be denied potentially life-saving treatment if the Draft Guidance is followed;** **(e) potentially opens up the NHS to the risk of discrimination allegations (on the grounds of race) – given the greater prevalence of HCV sufferers with Genotype 4, 5 or 6 within communities where the HCV patient is a British subject of African (including Egyptian) or Asian descent (compared to Genotypes 1, 2 and 3); and** **(f) potentially opens up the NHS to the risk of discrimination allegations (on the grounds of disability) – given the greater incidence of Genotype 4, 5 or 6 within the Haemophilia community (particularly where the HCV infection was caused by NHS contaminated blood products which were imported from abroad), again compared to Genotypes 1, 2 and 3.** Paragraphs (d) to (f) above are challenging for me to make, on one level, as somebody who has relied throughout my life on the fantastic care and treatment by so many in the NHS. They are observations that are not intended to be threatening. They are made because in Appendix B of the Draft Scope relating to Sofosbuvir published by NICE in June 2013, NICE specifically requested (at p6):	Comment noted. Haemophilia Alliance, the Haemophilia Society, the Transplant Support Network, and NHS Blood and Transplant were included in the matrix and invited to participate as consultees and commentators in this appraisal; none chose to participate in the appraisal. The Committee considered the potential equality issue raised regarding disproportionate representation of people with genotype 4 HCV and haemophilia. The Committee noted that the distribution of HCV genotypes in people with haemophilia presented by the company was actually similar to the overall population of people with HCV in England and was therefore not an equalities issue. The Committee also considered comments from consultees on the NHS cost of treating people co-infected with haemophilia and that treating HCV in this population could be cost saving. Having taken into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, the Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin

Role*	Comment	Response
	"In particular, please tell us if the proposed remit and scope: • ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Sofosbuvir will be licensed;*** • ***could lead to recommendations which have a different impact on people protected by the equality legislation than on the wider population e.g. by making it more difficult in practice for a specific group to access the technology;*** • ***could have an adverse impact on people with a particular disability or disabilities."*** It is my opinion that the Draft Guidance has failed to consider each of these, in the context of Genotypes 4, 5 and 6 in particular. **Background** In the late 1970s and 1980s, over 4800 British Haemophiliacs were infected with Hepatitis C through contaminated blood as part of their NHS treatment. A further 170 British non-Haemophiliacs were also infected with Hepatitis C through contaminated blood received as part of NHS treatment. Many of those were also co-infected with HIV. A significant number of those infected have since passed away. While bodies such as the Skipton Fund and Caxton Foundation have offered some financial recompense for HCV sufferers who were infected through contaminated blood products received from the NHS, this remains a great tragedy in the history of the National Health Service. I am a male with Severe Haemophilia A, with inhibitors. I acquired HCV through contaminated blood products as a youngster. I was formally diagnosed in 1991 with Genotype 4. Earlier this year, I was diagnosed with Cirrhosis. I have previously (in 2011) received 48 weeks' treatment with Interferon & Ribavirin (during which I successfully cleared the virus in 2012, only to find that I had later relapsed). **The QALY, other Health Benefit and wider NHS Cost Argument** In Appendix B of the Draft Scope relating to Sofosbuvir published by NICE in June 2013, NICE specifically requested (at p6): ***"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 within the QALY calculation?"***	for treating people with genotype 4, 5 or 6 treatment-naive HCV who have cirrhosis could be considered a cost-effective use of NHS resources. The Committee noted that the

Role*	Comment	Response
	In the context of Haemophiliacs, the answer is a resounding yes. Please note – The Committee considered the full response from this individual but for the purposes of this consultation table personal information related to the commentator has been redacted. . For Haemophiliacs who suffer from HCV, regardless of their Genotype, then it is clear that Sofosbuvir has **potentially significant and substantial health related benefits that are unlikely to be included within the QALY calculation**. And potentially huge future cost savings to the NHS when compared to not curing HCV in a Haemophiliac patient. This letter is on behalf of all Haemophiliacs and Contaminated Blood Sufferers, who have HCV.	clinical trials excluded patients with haemophilia and no clinical evidence or cost-effectiveness analysis had been presented specifically for people with haemophilia and HCV. Therefore the Committee concluded that no evidence-based decision or modelling would be possible, and therefore no separate recommendation could be made specifically for this patient group.
	Conclusion Where the clinical efficacy of Sofosbuvir has been accepted by NICE, for any particular Genotype, I believe that NICE should recommend, within its final guidance, that Sofosbuvir should be prescribed to all HCV sufferers regardless of Genotype, prior treatment experience or cirrhotic condition. This would mirror the position in Scotland, be equitable from an equalities legislation perspective, though go beyond the current recommendation in the Draft Guidance, for patients with Genotypes 4, 5 or 6. If NICE feels unable to reach that conclusion, then NICE should – at the very least – recommend the following as an exemption to its proposed general recommendation in relation to Genotypes 4, 5 or 6. **"Where the clinical efficacy of Sofosbuvir has been confirmed by NICE for any particular Genotype (including, for this purpose, Genotypes 4, 5 and 6), and the prescribing of Sofosbuvir would:** **(a) lead to potential significant and substantial health benefits for patients with a particular disability or disabilities in addition to HCV (such as Haemophilia); or** **(b) avoid the potential for a future increased cost burden on the NHS resulting from complications in treating that HCV patient, due to that existing disability (a future cost burden to the NHS with that patient group which could be otherwise reduced by curing HCV),** **then NICE recommends that Sofosbuvir should be prescribed to those HCV patients with that particular disability or disabilities (such as Haemophilia) regardless of Genotype."**	Comment noted.

Role*	Comment	Response
	I look forward to receiving the support of the recipients to this letter and I sincerely hope that NICE will take account of the points I have raised when they publish their final guidance	
Patient organisation	Positively UK welcomes and endorses the NICE appraisal for Sofosbuvir for treating chronic hepatitis C. Positively UK is a registered charity supporting over 1,000 people living with HIV every year, many of whom are co-infected with Hepatitis C. We agree with the preliminary recommendations for the use of Sofosbuvir as summarised on pages 3-5 of the appraisal document. We particularly welcome the recommendation for Sofosbuvir in treating patients co-infected with HIV and Hepatitis C. People living with these conditions are met with stigma. We believe the availability of such medications will tackle some of this stigma, encourage people to seek earlier diagnosis and be treated. For people living with HIV, and at risk of additional co-morbidities, it will ensure access to the best quality care and in improved quality of life. With Sofosbuvir also approved for use in Scotland, the NICE appraisal, will ensure equitable access to care and treatments across the UK. In declaring interests Positively UK do receive core funding from Gilead Sciences, which account for no more than 2% of our annual turnover.	Comment noted.

A response of no comment was received from the following organisations: Department of Health, MSD, Royal College of Nursing, Royal College of Pathologists