The British Viral Hepatitis Group and the British Association for the Study of the Liver would like to comment on the Appraisal Consultation Document on Sofosbuvir for treating chronic hepatitis C. We note that specific comments are required:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The provisional outcomes and decisions appear robust and thorough, and we congratulate the NICE committee and Expert Review Group (ERG) on the work done to date.
There are however several points that we would like to raise:

1. We believe that Sofosbuvir (SOF) is likely to prove an important antiviral therapy for hepatitis C, given its potency, safety, genotypic activity (particularly across genotypes 1, 2, 4, 5 and 6) and high barrier to resistance.
2. We agree that the lack of comparator arms in the majority of studies is a data gap, which makes it difficult to construct a mixed treatment comparison. Understandably (for the NICE process) this makes the estimation of efficacy and relative benefit difficult to accurately quantify. However it is the view of BVHG and BASL that SOF is a significant therapeutic advance for many patient groups. The increased SVR rates with SOF/PEG-IFN/RBV in naïve genotype 1 patients compared to the results obtained with the current standards of care (PEG-IFN/RBV, or 24-48 weeks of Telaprevir/PEG-IFN/RBV or Boceprevir/PEG-IFN/RBV) are highly unlikely to be biased by patient selection or specific participant characteristics.
3. Inclusion of 48 week IFN-containing or IFN-containing plus DAA control arms would have significantly prolonged the phase 2 and 3 programs and therefore delayed ultimate access to this important medication for patient subgroups in great need.
4. There is a lack of a substantive body of data of efficacy in treatment experienced (TE) patients with genotype 1 infection with or without cirrhosis. The efficacy of SOF/PEG-IFN/RBV for 12 or 24 weeks in TE patients has been modeled, and a marketing authorization for TE genotype 1 patients was granted based on these extrapolations. Genotype 1 TE patients without cirrhosis can expect high SVR rates based on the combination of SOF/PEG-IFN/RBV. There is an important need for an effective regimen for these patients. It is believed likely that SOF/PEG-IFN/RBV for 12 weeks will prove relatively less efficacious in genotype 1 patients with cirrhosis and non-favorable IL-28B genotype, particularly in prior partial- or null-responders to interferon. The exact decrement in efficacy is unknown, as is the place of 24 weeks versus 12 weeks of the regimen and the future options for genotype 1 TE patients.
5. The division of patients into cirrhotic and non-cirrhotic groups is a reasonable division based on the sensitivity, specificity, and true- and false-positive rates

for cirrhosis of the available non-invasive methodologies, particularly transient elastography (Fibroscan), APRI or ELF testing. Stratifying patients in this manner is, and will remain, standard clinical practice.

6. Similarly the division of patients into treatment-experienced and treatment-naïve is a standard clinical process and logical for this appraisal.
7. The ratio of men to women in the manufacturer analysis should be adjusted to reflect the gender ratio of HCV infected persons in the UK
8. We note the detailed cost-effectiveness and economic model structure submitted by the manufacturer and revised by the ERG. A large body of data has been submitted and we trust that we are interpreting the findings correctly. We note particularly the data on extended (24 week) treatments.
    a. From table 13 the ICERs for SOF for genotype 1 treatment naïve (TN) SOF/PEG-IFN/RBV 12 weeks interferon eligible (IE) were £14,930, £11,836 and £7,292 versus PEG-IFN/RBV and telaprevir or boceprevir respectively and thus the regimen seems cost effective. However this does not appear to be the case from the figures presented for SOF/RBV for 24 weeks in genotype 1 interferon unsuitable (IU) patients
    b. No case was made for the cost effectiveness of SOF/PEG-IFN/RBV in TE genotype 1.
    c. For genotype 2, the ICERS appeared to be within acceptable thresholds for genotype 2 TN IU, TE IE, and TE IU.
    d. For genotype 3 the ICERS are within acceptable thresholds for 12 weeks SOF/PEG-IFN/RBV in TN IE, and TE IE but were higher for the 24 weeks regimens in the TN IU and TE IU. Thus treatment appeared cost-effective for genotype 3 patients treated for 12 weeks.
    e. For genotype 4, 5 and 6 similar cost effective ICERs were noted for SOF/PEG-IFN/RBV 12 weeks.
9. The ERG probabilistic sensitivity analysis suggests a high likelihood of the ICER being within the cost effective thresholds:
    a. For SOF/PEG-IFN/RBV 12 weeks in genotype 1 TN IE
    b. For genotype 3 TN IE, SOF/PEG-IFN/RBV (12 weeks) (at the £30,000 threshold)
10. We note the trend in the revision table produced by the ERG which in general corresponds to the trend noted above, including table 22 which recalculates the ICERS based on a weighting of 61% men.
11. Thus there are groups that receive 12 weeks SOF/PEG IFN/RBV in whom the ICERS do suggest a cost-effective therapy.
12. In reality the uptake of the less cost-effective regimens with 24 weeks SOF/RBV or PEG IFN/SOF/RBV for genotype 1 infection will be low while waiting for SOF/ledipasvir regimens to become available. The NHS England commissioning process for urgent treatment will provide access for many patients.
13. An exception may have to be found for a small subset of genotype 3 patients who require an IFN-free regimen of SOF/RBV for 24 weeks.
14. In summary we support that SOF should be made available for patients requiring treatment and in whom treatment is cost-effective.

15. We are not in agreement that most clinicians would be likely to utilize 24 weeks of SOF/RBV for G3 patients. Data from the Boson study are not presently available, but it is our view and understanding that the majority of clinicians will likely utilize 12 week PEG-IFN/SOF/RBV for the vast majority of genotype 3 patients, and in the small subset who are truly IU, potentially a 16-24 week SOF/RBV regimen. Many of the latter patients however, unless in urgent clinical need, will probably be advised to await newer treatments rather than utilize prolonged SOF/RBV.
16. For the small subset of genotype 3 TE patients who cannot take IFN, we would strongly encourage discussions with the manufacturer on initiatives such as a cost per SVR, or a charge for 12 weeks of SOF with provision of SOF for 24 weeks
17. It is unlikely that a large number of patients with genotype 1 will require 24 weeks of SOF and RBV as improved treatments for TE genotype 1 patients are imminent:
    a. We are aware that SOF and daclatisvir or ledispavir are not considered in this appraisal and the remit and decision problem were to appraise SOF within its licensed indication for hepatitis C. Unfortunately the currently considered data does not take into account near future options which already have a bearing on clinical decision making. Recent phase 3 data has shown that the combination of SOF and an NS5a inhibitor, i.e. SOF/daclatasvir or SOF/ledipasvir, is highly effective in patients with prior non-response to PEG-IFN/RBV or prior non-responders to either telaprevir or boceprevir.
    b. A 12 week SOF/ledipasvir regimen was effective in > 90% of TE patients, (although prior non-responders with cirrhosis may have benefited from 24 weeks). These data greatly cloud the issue for clinicians who may elect to defer patients for a future non-interferon containing DAA regimen rather than a 24 week SOF + RBV course. Thus the real costs to the NHS are not based on the use of SOF + RBV for 24 weeks but the hopefully similar costs of SOF/ledispasvir for 12 weeks (and perhaps, in rare cases, for 24 weeks). This should be taken into account when weighing up the costs to the NHS. Indeed the NHS has already put in place interim commissioning arrangements for SOF plus an NS5a inhibitor, for example ledispasvir, for patients at significant risk of death or irreversible damage.
18. Some potentially important data is missing from the document – specifically further data on HIV co-infected individuals (1910 study).
19. The value of cure in patients without cirrhosis but with symptoms of hepatitis C will need to be addressed by NICE and by NHS England and commissioners in Wales.
20. The public health benefits of cure – preventing onward transmission – should be addressed in future appraisals.
21. The shorter duration of treatment for higher SVR rates is a great advantage in the clinical management of patients. The reduced number of interventions, including monthly visits, and reduced need for ancillary measures for

managing side effects, particularly anaemia and cytopaenias, will be significantly advantageous.

22. The relative lack of significant drug-drug interactions is also a significant advantage for SOF, particularly in those with multiple co-morbidities.
23. An important issue is that of specific subgroups who are sociologically disadvantaged. The Consultation Document comments that access for such patient groups is related to implementation and not a technology appraisal. However we believe that the shortened treatment durations and markedly improved adverse event profiles in certain subgroups significantly impact on certain disadvantaged groups, for example people with injecting drug use and therefore acknowledgement and some discussion of this would be appropriate. Another example is those in offender institutions (e.g. prison), where oversight from healthcare staff may be less than other settings, and where patient transfers may significantly impact on the ability to complete prolonged treatment regimens. It may be appropriate to allow or direct clinicians to consider these factors when deciding on treatments.
24. Lastly it is gratifying that recognition has been taken of the patient representatives and potential patient voice. Though this should not directly affect the decisions of the NICE committee it is important to appreciate the context - SOF is the first new agent for G2 and G3 patients in over 15 years, and therefore the first new hope to some patients who have failed or been intolerant of previous standard-of-care; and, though the SMC decision-making process is different from NICE, patients may find it hard to understand discrepancies of guidance (and ultimately access) across borders within the UK.

We would like to strongly urge the committee to allow clinicians in England and Wales to have access to SOF as part of our increasing armamentarium for battling hepatitis C; something which ultimately will bring significant health benefits and cost-savings to the NHS. The drug is cost-effective for many patients, and negotiation regarding the costs of exceptional use of SOF/RBV for 24 weeks, particularly in genotype 3 TN or TE IU patients, could be sought from the manufacturer.

We thank the committee again for the opportunity to comment, and congratulate them on the work completed to date.