BRITISH SOCIETY OF GASTROENTEROLOGY | BASL British Association for the study of the Liver | BVHG British Viral Hepatitis Group | The Royal College of Pathologists Pathology: the science behind the cure

'NHS England Submission To Questions Raised By NICE Following Consultation Responses To Hepatitis C Drug Appraisals'

The British Society of Gastroenterology, British Viral Hepatitis Group, British Association for the Study of the Liver and Royal College of Pathologists are grateful to the NICE Appraisal Committee for allowing us to respond to comments received from NHS England with regards to the following treatments for hepatitis C:

- sofosbuvir/ledipasvir
- daclatasvir
- paritaprevir/ritonavir, ombitasvir and dasabuvir

Summary of the organisations responses to specific NHS England points

- Lack of evidence of effectiveness

We disagree with NHS England's assertion that there are significant gaps in the evidence base and stand with NICE in its decisions

- Lack of evidence of cost effectiveness

The evidence for cost effectiveness is clear and the additional data alluded to in NHS England's submission increases, not decreases the cost effectiveness of therapy

- Need for multiple technology appraisal

This mechanism would be too slow, would potentially exclude some suitable therapies, and is inappropriate in a fast moving therapeutic area. NICE guidelines and outcome monitoring are a more appropriate way forward using NICE judgements from the current STAs as the base case

- Lack of consideration of a wait and watch approach for those with less severe liver disease.

This is unsafe clinically as the tools for diagnosis, for monitoring frequency and a recall system are lacking. It has also been previously assessed by NICE as being suboptimal on both cost effectiveness and clinical grounds.

- Budgetary impact and affordability

NHS England's arguments are based on wholly inappropriate interpretations of the numbers of patients aware of their diagnosis and who are likely to access therapy and be treated each year. We contest that the true figures are highly affordable and represent excellent value for NHS England

- Role of NICE and the NHS England challenge

We believe that if upheld, this challenge to NICE by NHS England would fundamentally alter NICE's role and remit. This would potentially lead to a situation where NHS England's veto on the ground of potentially spurious claims of unaffordability would deny not only hepatitis C sufferers but people with other serious clinical conditions access to highly cost effective therapy.

The NHS England submission.

NHS England have submitted a series of arguments to NICE to evidence their contention that NICE should not approve the 3 current STAs ongoing.

These arguments are summarised as:

1. The evidence base for the interventions is inadequate, specifically in hard to treat patients, those currently not engaged in treatment where the risk of reinfection is unclear and the omission of watch and wait strategies for those with mild liver fibrosis
2. The cost of implementing NICE guidance for these 3 drug regimens would be unaffordable.

The organisations above, who represent a broad spectrum of clinicians involved in diagnosing and treating hepatitis C infection in England, feel the arguments cited have no validity and solely represent an attempt by NHS England to both constrain costs at the expense of patients' health in an area of existing significant health inequalities, and undermine the vital role of NICE in setting an objective benchmark for treatment cost effectiveness and fitness to become standard NHS therapy.

Evidence supporting effectiveness and cost effectiveness.

To deal with specifics in the NHS England response relating to the evidence, NICE has an established and robust process for assessing the evidence and no substantial gaps were identified which would not allow an assessment of cost effectiveness to be undertaken. The levels of evidence for each specific patient group are extensively addressed across the three STAs and the clinical community believes this data is as robust as any other area of recent medical therapeutic advance. The evidence cited by NHS England as areas of gaps are not so, with perhaps a single exception. Indeed the data cited by NHS England in their submission specifically undermine their argument. All the data for Sofosbuvir/Ledipasvir confirm that short duration therapy (12 weeks versus 24 weeks) is effective which makes the new agents more cost effective than the base case taken by NICE. The cited specific gap of evidence for effectiveness in those with advanced liver disease is inaccurate and incorrect – sufficient data is available and indeed some of this has come from access policies funded by NHS England. The Sofosbuvir Early Access Programme for those with severe or decompensated disease was a significant success and is the one area where clinicians felt that there was a genuine partnership between NHS England and those delivering treatment to a high needs group. This major programme demonstrated that the drugs assessed in two of the three STAs are highly effective even in this patient population. The other specific area of evidence where NHS England are incorrect is genotype 3 infection where the UK based BOSON study has provided clear unambiguous answers.

The clearly carefully selected edited commentary by the hepatitis C CRG/CAG also appears at odds with NHS England's interpretation. This direct misrepresentation by NHS England of any consensus CRG/CAG view has resulted in one member of the CRG/CAG resigning on principle. The clinical community regard the CRG/CAG's comments as emphatically in support of treatment with the new agents in line with NICE provisional approvals. We hope and expect that CRG members, some of whom have not been able to discuss the situation and their views with the rest of the clinical community because of signed confidentiality agreements with NHS England, are able to present a

full view of their opinions to NICE. We have no doubt they will support the provisional approvals issued by NICE in full.

This degree of certainty over the correct choices of treatment was ratified by a consensus meeting proposed and supported by NHS England where, in the light of NICE draft STA guidance and additional evidence that had become available, the optimal regimens were agreed (the document is attached as an appendix to this letter). This process clearly had the stamp of approval of NHS England and it is again perverse to suggest that having initiated this, NHS England now do not accept there is a clinical consensus supported by a strong evidence base for these treatments.

The only area where the specialist societies are in some agreement with NHS England over the evidence base is the expansion of treatment into areas where patients currently have lifestyles which would not allow interferon based therapies. In this setting uptake, completion rates and reinfection have uncertainties. This is an area where commissioning for evaluation may have a place as may formal research projects. Indeed NIHR are shortly considering the funding of a study examining initiatives in this very specific patient group (Chief investigator [redacted]), and the Chief Investigators (Profs [redacted], [redacted]) of a Department of Health Policy Research grant have approached NHS England to ask for access to all oral DAAs for the treatment of clients attending substance misuse services as a research exercise.

It is important to consider however the current structure of services in regard to this. Seventy percent of hepatitis services do not have outreach sites in substance misuse services currently, based around the poor uptake of interferon based therapies in this patient population. There is overwhelming evidence that patients in these settings do not access secondary care and therefore this patient group represents a substantial proportion of those currently tested and known to be positive who have not accessed treatment. There is no reason to suspect that lifestyle factors which stop hospital attendance for assessment will differ from those which would stop people taking up oral treatments so treating this population will requite establishment of outreach services in locations they can and do attend. To establish these services will take time, presumably a function of the new hepatitis C networks. Given however that the funding mechanism for networks, outside some pump priming for data gathering and pharmacy support, is likely to be negligible, it seems certain that any expansion of outreach will be a slow and therefore highly controlled one with little short or medium term impact on NHS England's budget. It is salutary and informative in this regard to note that opt out testing in the prison population has only just been rolled out and there remains a substantial gap in the delivery of treatment in prisons which will likely take a number of years to close.

Multiple technology appraisal.

NHS England suggest that given the number of agents being considered by NICE an MTA would be the appropriate method of assessing these agents. There is a comment that 'all stakeholders who have advised NHS England' have indicated the importance of MTA in this disease area. We are not clear on who these stakeholders are as there have been no approaches to any of the specialist societies. The argument is fallacious, in a rapidly moving area with new agents likely to enter clinical practice an MTA would be too slow, would not be able to consider newly available agents, and would be rapidly outdated. We assert that a NICE-accredited guideline approach as for HIV therapy

is a far more effective and appropriate way of managing these new introductions within the cost effectiveness envelope established by NICE.

Wait and watch approach for patients without severe fibrotic liver disease.

NHS England contend that a wait and watch approach should have been a comparator in the STA assessment process. We believe this is not a safe or cost effective clinical path to follow. There is a clear evidence base assessed by NICE which mitigates against a wait and watch approach. Since the advent of ribavirin the cost effectiveness of treating over waiting for liver fibrosis to develop has been clear, leading to recommendations that all patients irrespective of liver disease severity should be treated. NHS England produces no data to suggest that this well established principle, one produced with drug treatments which had a cost not dissimilar to the oral agents included in the STAs, should be abandoned.

The NHS England proposal to address this is also unworkable in practice. An arbitrary F3 fibrosis level for treatment initiation has a number of significant practical problems. Liver biopsy solely for this purpose is impractical, unethical and unacceptable to patients and the non-invasive technologies available have a poor evidence base for such a distinction and are not widely available in the UK. Many liver and infectious diseases centres in England as well as most smaller units do not have access to elastography. There is no evidence base to suggest a reasonable time frame for repeat of such testing in those who have a score below such an arbitrarily defined threshold and there are no robust mechanisms of any sort to ensure adequate recall for patients. It is the contention of the clinical community that given these key uncertainties it is impossible for NHS England to safely adopt a wait and watch process now or in the medium term.

Budgetary impact of the new agents: affordability.

NHS England's view of the budgetary challenges hepatitis C drugs may pose is simplistic and wrong both in terms of factual information and the principles of equity and fairness.

There are a number of models of the UK hepatitis C epidemic, some produced and validated by Public Health England (PHE). In the PHE models of impact the key assumptions are based on both the figures held by PHE and full engagement with clinicians to understand the barriers to diagnosis and treatment and what may be possible to deliver to reduce the burden of end stage liver disease. Even with the most aggressive case finding and treatment scenarios from PHE treating more than 10 000 people per year is highly unlikely, and it should be borne in mind that even this figure is three times that achieved currently. There are a number of reasons why NHS England's worst case scenario is incorrect. Firstly the figures they quote assume that all patients estimated to be living with hepatitis C in England are aware of their diagnosis which is incorrect. PHE estimates that possibly 60% are diagnosed. This dramatically reduces NHS England's predicted impact in the absence of some sort of national case finding strategy for which there is no current plan. We also know a significant number of people have disengaged with services and many have not engaged at all, estimated to be another 20-30%. The idea that suddenly all these individuals will come forward for treatment is fanciful, the reality is that clinical services will have to work hard to find them and this will take time.

Even considering those patients who are engaged with existing services the figures proposed by NHS England are not realistic. The potential numbers able to be treated are also determined by the present treatment capacity within the NHS. Each course of antiviral therapy with these antiviral

drugs requires 7 outpatient attendances with an experienced, trained hepatitis specialist and a review at a multidisciplinary meeting. Treating 80,000 patients (involving 560,000 extra outpatient visits and 13,000 hours of MDT discussion) is unrealistic within the timeframes that have been suggested.

In the initial year the clinical capacity issue has been exacerbated by the very significant delays in the commissioning policy statement for cirrhotic patients from NHS England. Despite NICE ruling that this should have been available from April 2015 it was finally signed in the second week of June. This delay has led to an increased backlog of patients with cirrhosis that should be treated in the initial wave. This limits access for others.

Funding Hepatitis C drugs and impact on other specialised commissioned services

NHS England's contention that funding hepatitis C drugs will displace other more effective treatments is particularly noteworthy. Few health interventions offer cure, fewer still in more than 90% of people affected and as an investment for the Nation hepatitis C therapy is highly cost effective. Further the quoted impacts on the wider health system suggested by NHS England are based on an unpublished draft paper which is not available for scrutiny, and a further article which has been incorrectly referenced and therefore similarly not available for review. Also unacknowledged by NHS England is that from August 2015 sofosbuvir, peg-interferon and ribavirin will be commissioned (as per previous NICE STA) for all those with genotype 1 disease and some other patients with different genotypes. The products presently under review by NICE are similarly effective and cheaper than this therapy when utilised within clinically acceptable 8-12 week regimens and therefore are actually cost-saving to NHS England, rather than the converse which is being proposed.

NHS England has choices about where it may invest and where it may make savings in a very substantial drug budget. To compare the cost impacts of a new technology solely to the expected growth in funding is unbalanced, as costs are fluid within the health system with new innovations, advances, the greater availability of generics etc. It would rather be more valid to compare any cost pressures to their total budget. NHS England also chooses in its submission to play off the discounted costs of current treatments for hepatitis C which it quotes as the comparator, against the list prices of the new agents. There are clear savings to be made with these new drugs which NHS England does not appear to be willing to include in its calculations although it is universally acknowledged that these will emerge. We do not believe that a sensible approach to funding NICE approved hepatitis C drugs will disadvantage other similarly cost effective therapies. It is perhaps of note in this regard that there appear to be incorrect financial calculations provided by NHS England – for example in the ledipasvir STA response they quote that treating 50% of 6000 patients with cirrhosis would cost £121 million, however 3000 treatments at the full list price of £38 980 would be £117 million, not the inflated figure quoted.

NHS England comment on the difficulties of in-year budget adjustments. It is important to state clearly that NHS England has been aware for the last two full financial years that these treatments were likely to have received European Medical Agency approval and were on the programme for NICE approval, as well as having estimates of their costs. We therefore fail to understand why no budgetary plans have been put in place to deliver these treatments prior to part way through this financial year.

NHS England suggest that the ICER thresholds should be adjusted. To our knowledge the setting of the ICER thresholds is a matter for NICE, the Department of Health and wider society, not national commissioners and we believe NHS England have overstepped their authority in making such statements.

Clinical and patient partnerships in new drug allocation

An important comment is that clinicians and patients are reasonable people who respond to reasonable things. We are used to working in resource limited environments and managing budgets. Patients understand that a treatment that costs £30 000 will be subject to limitations on speed of access and appreciate that some degree of prioritisation is likely to be required. Arbitrary decisions over treatment based on a total misunderstanding of the need are unlikely to be as effective a way of managing budgets as a dialogue between informed patients and clinicians over clinical need. NHS England would benefit significantly from understanding this.

NHS England's challenge and the broader impact on NICE

The NHS England approach in challenging NICE on the grounds of affordability, particularly with spurious costs and unrealistic projections, is potentially hugely damaging. If this challenge were to go through there is no role for NICE, NHS England would not have to justify its budget allocations in future other than by claiming that any new development, on however arbitrary grounds, was unaffordable. The unanimous view of the clinical organisations who are signatories to this letter is that these objections are unfounded and should not be allowed to stop the approval by NICE of the three STAs on new hepatitis C agents or any other subsequent drugs assessed by NICE.

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APPENDIX

Recommendations from Consensus Meeting on Therapy for Chronic Hepatitis C
London March 3 2015

Background

The treatment options for patients with chronic hepatitis C are expanding rapidly. To guide clinicians and commissioners the national societies (BASL, BHIVA BIA, BSG, BVHG) representing clinicians with an interest in this area convened a meeting to provide evidence based treatment and management recommendations.

Methods

A nominated individual outlined the background data (both published and outcome data from the English early access program) and presented proposals for therapy. These were discussed by the 80 attendees and a consensus was reached. This document outlines the consensus recommendations.

Treatment recommendations:

Genotype 1 - Patients with no evidence of cirrhosis/severe fibrosis

For patients who are treatment naïve preferred treatment is with all oral direct acting antiviral regimens. The following options are all acceptable on efficacy and safety criteria:-

Sofosbuvir/Ledipasvir+/- ribavirin*	8 weeks
Ombitasvir/Paritaprevir (r)/Dasabuvir +/- ribavirin*	12 weeks
Sofosbuvir/Simeprevir	12 weeks
Sofosbuvir/Daclatasvir	12 weeks

If oral DAA regimens are not funded for this patient group by the NHS, patients have the option of waiting for oral therapy, self-funding or starting treatment with an interferon-based regimen.

Interferon based regimes include:-

Sofosbuvir/PEG-interferon/Ribavirin	12 weeks
Simeprevir/PEG-interferon/Ribavirin	
G1b or G1a without Q80K variant	12 weeks plus 12 or 36 weeks PEG/RBV

For patients with G1a who are Q80K variant positive simeprevir based regimes are not recommended.

Genotype 1 Patients with compensated cirrhosis/severe fibrosis/major extra-hepatic manifestations

Preferred treatment is with all oral direct acting antiviral regimens. The following options are all acceptable on efficacy and safety criteria:

Ombitasvir/Paritaprevir (r)/Dasabuvir +/- ribavirin*	12 weeks (Child Pugh A only)
Sofosbuvir/Ledipasvir+/- ribavirin*	12 weeks
Sofosbuvir/Simeprevir +/- ribavirin	12 weeks
Sofosbuvir/Daclatasvir +/- ribavirin	12 weeks

For all patients who have failed to achieve SVR with PEG-interferon/Ribavirin treatment is as above (i.e. as per G1 compensated cirrhosis). However for patients with genotype 1a virus, and previous null response to PEG-interferon/Ribavirin, treatment should be 24 weeks of Ombitasvir/Paritaprevir (r)/Dasabuvir/Ribavirin.

For patients who have failed to achieve an SVR with PEG-interferon/Ribavirin and a protease inhibitor treatment should avoid a protease containing regime and preferred treatment options are sofosbuvir plus ledipasvir OR sofosbuvir plus daclatasvir.

Genotype 1 - Patients with decompensated cirrhosis

Treatment is recommended with oral Sofosbuvir/Ledipasvir +/- Ribavirin for a total of 12 weeks
**Strong consideration should be given to adding ribavirin, though individual patient decisions are to be made by MDT. For G1b patients without cirrhosis the licensed indication for AbbVie 3D does not include ribavirin*

Genotype 2 - Patients with no evidence of cirrhosis/severe fibrosis

Treatment naive
PEG-interferon/Ribavirin 24 /52 (12-16/52 in low viral load/rapid viral response)
Treatment experienced (previous PEG-interferon/Ribavirin), or IFN intolerant Sofosbuvir/ribavirin or those with extrahepatic manifestations 12/52

Genotype 2 - Patients with compensated cirrhosis/severe fibrosis/major extra-hepatic manifestations

Treatment naive: Sofosbuvir/Ribavirin 12/52
Treatment experienced: Sofosbuvir/Ribavirin 12/52 (cirrhotics 16/52)

Genotype 2 - Patients with decompensated cirrhosis

Treatment is recommended with either
Sofosbuvir/Ledipasvir +/- Ribavirin for a total of 12 weeks

Sofosbuvir/Daclatasvir +/- Ribavirin for a total of 12 weeks

Genotype 3 - Patients with no evidence of cirrhosis/severe fibrosis

For patients who are treatment naïve preferred therapy is:-

PEG-interferon/Ribavirin for 24 weeks (12-16/52 in low viral load/rapid viral response)

For those intolerant of interferon – Sofosbuvir plus daclatasvir or ledipasvir +/- ribavirin for 12 weeks is recommended

For patients who are treatment experience preferred therapy is:-

PEG-interferon/Ribavirin /Sofosbuvir for 12 weeks

For those intolerant of interferon – sofosbuvir plus daclatasvir or ledipasvir +/- ribavirin for 12 weeks is recommended.

Genotype 3 - Patients with compensated cirrhosis/severe fibrosis/major extra-hepatic manifestations

Preferred treatment is:-
PEG-interferon/Ribavirin /Sofosbuvir for 12 weeks

For those intolerant of IFN the following treatment options are all acceptable:-

Sofoabuvir/daclatasvir/ribavirin for 12 weeks
Sofosbuvir/ledipasvir/ribavirin for 12 weeks
Sofosbuvir/ribavirin for 24 weeks

Genotype 3 - Patients with decompensated cirrhosis

Treatment is recommended with either
Sofosbuvir/Ledipasvir +/- Ribavirin for a total of 12 weeks

Sofosbuvir/Daclatasvir +/- Ribavirin for a total of 12 weeks

Genotype 4 - Patients with no evidence of cirrhosis/severe fibrosis Non-cirrhotic G4 patients

Preferred treatment is for 12/52 therapy with all oral direct acting antiviral regimens. The following options are all acceptable on efficacy and safety criteria: choice to be determined by NICE approval, availability of funding from NHS England, and local MDT choice:

PEG-interferon/Ribavirin /Sofosbuvir for 12/52
PEG-interferon/Ribavirin/Simeprevir for 12/52 with PEG-interferon and ribavirin for a further 12 weeks
Ombitasvir/paritaprevir/ritonavir/ribavirin for 12/52
Sofosbuvir/Ledipasvir/ribavirin for 12/52

Genotype 4 - Patients with compensated cirrhosis/severe fibrosis/major extra-hepatic manifestations

Sofosbuvir/Ledipasvir/ribavirin for 12/52

Should none of the options above be available, patients wishing to be treated should be offered Simprevir/PEG-interferon/ribavirin with 24-48 weeks therapy (response guided therapy)

Genotype 4 - Patients with decompensated cirrhosis

Treatment is recommended with either
Sofosbuvir/Ledipasvir +/- Ribavirin for a total of 12 weeks
Sofosbuvir/Daclatasvir +/- Ribavirin for a total of 12 weeks

Liver transplant patients

Evidence of fibrosis post-transplant should mandate therapy as current data suggest that earlier treatment delivers comparable outcomes to non- transplant, non-cirrhotic populations. Therapy options can impact on immunosuppression thus monitoring and therapy should be delivered by, or in close collaboration with a transplant centre. Peg-interferon can precipitate graft rejection and its use can no longer be justified for the majority of transplant patients.
Options:

G1 sofosbuvir/ daclastavir +/- ribavirin – 12 weeks
sofosbuvir/ ledipasvir +/- ribavirin – 12 weeks
ombitasvir/paritaprevir (r)/dasabuvir/ribavirin 24 weeks
sofosbuvir/ simeprevir +/- ribavirin- 12 weeks

G3 sofosbuvir/ daclastavir +/- ribavirin – 12 weeks
sofosbuvir/ ledipasvir +/- ribavirin – 12 weeks

G4 sofosbuvir/ ledipasvir +/- ribavirin – 12 weeks
ombitasvir/paritaprevir/ritonavir/ribavirin- 12 weeks

Cirrhotic post –transplant are a small population and treatment should be individualized – ie no recommendations can be made due to a paucity of data

Other general recommendation:

- It is strongly recommended that all patients starting DAA therapy have a baseline plasma sample archived in the event of treatment failure. All patients with DAA failure should have a sample tested for relevant resistance on the first sample following failure
- Whilst currently treatment recommendations for HIV+ patients are the same as for HIV negative patients, this may change with emerging data. Furthermore the choice of therapy will need to be guided by potential for drug-drug interactions with HIV therapies (see http://hep-druginteractions.org/). All HIV co-infected should be managed jointly with experts in managing co-infection
- It is recommended that consideration is given to embedding strategically important research questions into the specialist commissioning process

Diagnosis of cirrhosis

The following working definition of 'cirrhosis/advanced fibrosis' was agreed for the sole purpose of including all/most patients likely to have cirrhosis due to hepatitis C* into the treatment algorithms proposed. Any one of the measures listed will suffice:

- Liver biopsy with stage 5/6 fibrosis or METAVIR 3/4
- Imaging evidence of cirrhosis (either US, CT or MR scan)
- APRI >2 and AST:ALT>1 on at least two occasions
- Evidence of established portal hypertension (varices or ascites) excluding non-cirrhotic or other causes
- Fibroscan elastography score >11.5 (or equivalent ARFI)

*where the patient has other risk factors for cirrhosis it will be for clinical judgement to consider the relative contribution from HCV and potential impact of treatment