About you

Your name: Dr Charles Millson

Name of your organisation: British Society of Gastroenterology (BSY)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **No**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **Member of BSG (Liver Section)**
- other? (please specify)

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are around 215,000 individuals in UK infected with Hepatitis C virus (HCV). A significant proportion of patients will have acquired their HCV from intravenous drug use, currently or many years ago. Others will have been infected from blood products or in healthcare settings overseas, hence a significant proportion of migrants from Pakistan, India, North Africa and Eastern Europe also have the infection. The virus was identified in 1989 and tests were available from 1991.

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Treatment for HCV was based on Interferon, progressing to Pegylated Interferon and Ribavirin in early 2000's. The first generation of Directly Acting Anti-virals (DAA's) were NICE approved in 2012. Bocepravir and Telaprevir improved the overall cure rate of PEG-Interferon and Ribavirin from around 50% to over 60%. However,all Interferon based therapies are limited in their tolerance by patients by virtue of their side-effects. A majority of patients experience significant headaches, flu-like symptoms and low mood. Many patients cannot tolerate the therapy and in addition a significant amount of input is required from clinical nurse specialists to support the patients, watch for life-threatening haematological side-effects and generally encourage them to complete the course. More recently, Simeprevir (TA331) has been recommended by NICE for management of certain subtypes of the virus (genotype 1 and 4). This combination has a high success rate at curing the virus, but requires either 24 or 48 weeks of PEG-Interferon, with all the known side-effects. Sofosbuvir (TA330) has also been reviewed by NICE and recommended (February 2015) for the common subtype (genotype 1) in conjunction with PEG-Interferon and Ribavirin, and also under some limited circumstance for other sub-types. Whilst NICE has allowed some patients to receive Sofosbuvir with just Ribavirin, and not Interferon, the criteria are quite limited. Meanwhile, a combination of Sofosbuvir with another oral agent Ledipasvir (marketed as Horvani, and licensed in November 2014) is currently undergoing evaluation at NICE but will be an all oral therapy. In addition, other Interferon-free regimens incorporating the new agent Daclatasvir is undergoing a STA in combination, currently.

The current NICE approved treatments for HCV remain predominantly PEG-Interferon based. There is general consensus amongst specialists involved in treating HCV across the UK, at this moment in time, but there is variation in approach to how best to advise patients over uptake of treatment. Broadly speaking, the currently available Interferon based therapies are associated with significant side-effects and are generally poorly tolerated and offer a cure in most but not all, whereas new 'all oral' combination therapies are simple to take, have minimal side-effects and are considerably more effective in obtaining a cure.

Finally, the question of geographical variation is particularly relevant to HCV and the devolved nations. HCV is twice as prevalent in Scotland than England. The Scots have taken an 'aggressive' approach to the epidemic of HCV with both case-finding and provision of treatment. More patients have been treated and they have reported that they are already seeing an improvement in the long-term outcomes (liver cancer and liver failure requiring transplant etc).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
The natural history of HCV infection is that the virus causes ongoing inflammation in the liver, eventually resulting in scar tissue being laid down. Significant scarring leads eventually to cirrhosis and from there, liver cancer or liver failure can follow. 15-20% of patients will develop cirrhosis over a period of 20 years, and hospital admissions, deaths from liver disease, liver cancer and transplants related to HCV have all been steadily rising over the last decade.

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The Interferon-based therapies require a minimum level of liver function to enable the liver to withstand the 'insult' of the therapy. Patients with cirrhosis, do not have sufficient 'reserve' and their liver function will dramatically deteriorate with significant and sometimes fatal consequences. For this reason, patients with cirrhosis have a significantly worse prognosis compared with patients with less advanced disease. The relevance of this to the new technology is that these new all oral agents, which specifically do not incorporate Interferon are much better tolerated by the cirrhotic liver and the evidence is that the cure rate remains high.

Similarly, patients who have had liver transplants will all have recurrent HCV infection in their new livers. Whilst the new infection does not always cause injury, the combination of immune suppression and hepatitis C encourages the HCV, and high dose steroids, used to treat rejection post transplant, are particularly hazardous. Interferon-based therapies are associated with significant risk of organ rejection and the efficacy of such therapies is reduced in the immunosupressed patient. On top of this there are significant drug interactions. Recurrent HCV in a small sub-group of HCV transplanted patients (called Fibrosing cholestatic hepatitis) will die within 12 months of transplant and rarely is standard interferon therapy tolerated or effective.

Finally, patients with HCV and renal impairment or renal transplant do not tolerate ribavirin in standard doses and again can manifest rejection if post transplant. These patients need to be cleared of their HCV because they will be receiving immune suppression and yet the antiviral agents can prove potentially hazardous.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
The technology should be used, at present, within the established setting of the viral hepatitis service. These services are already embedded in Hepatology and Infectious Disease clinics and are supported by MDT's that include pharmacists, clinical nurse specialists etc. The best examples of these services include "out-reach" to prisons, satellite clinics, drug treatment centres etc. However, the toxic nature of Interferon-based therapies has meant that all such services have required significant support from the Hospital-based lead service. With the advent of all-oral regimes that are very effective and have minimal side-effects, one might expect that such therapies would become less and less 'dependent' on specialist centres and might devolve towards primary care/community settings. Indeed, it is likely that the combination of efficacy and tolerability will move the challenge of treatment away from current concerns of drug toxicity towards compliance and adherence.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
The technology has been licensed in UK for a few weeks only. Without guidance from NICE, there has been limited or no access to this drug within the NHS. However, there may be some experience from the Early Access Programme.

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Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

(A recent consensus meeting at Royal London Hospital, was due to report 13/3/15. No report yet available, but will be soon!)

1. Review Article: 2014 UK consensus guidelines - hepatitis C management and directly acting anti-viral therapy.
Miller MH[1], Agarwal K, Austin A, Brown A, Barclay ST, Dundas P, Dusheiko GM, Foster GR, Fox R, Hayes PC, Leen C, Millson C, Ryder SD, Tait J, Ustianowski A, Dillon JF; British Viral Hepatitis group; British Society of Gastroenterology Liver Committee; British Association for the Study of Liver; Scottish Society of Gastroenterology; Scottish Viral Hepatitis group; Scottish Viral Hepatitis Nurses group.
Aliment Pharmacol Ther. 2014 Jun;39(12):1363-75. doi: 10.1111/apt.12764. Epub 2014 Apr 22

Methodology: The working group were selected from members of leading hepatology and infectious disease societies, selected as leaders in their field. All Phase 2 and 3 studies, as well as abstract presentations from international Hepatology meetings were identified and reviewed for suitable inclusion, based on studies of new therapies in HCV. Treatment-naïve and experienced individuals, as well as cirrhotic and co-infected individuals were included.

Recommendations:
These were drawn up a year ago and are now unquestionably “out of date”

Recommendation: HCV genotype 1a-naïve patients should be treated with 12 weeks of interferon alpha 2a or b, with ribavirin and sofosbuvir, alternatively they could be treated with 12 weeks of simeprevir and 24 weeks of pegylated interferon alpha 2a or 2b and ribavirin or faldaprevir 120 mg for 12 weeks and pegylated interferon alpha 2a and ribavirin for 24 weeks (or 48 weeks under response-guided rules).

Recommendation: HCV genotype 1b-naïve patients should be treated with either 12 weeks of interferon alpha 2a or b, with ribavirin and sofosbuvir, or treated with 12 weeks of simeprevir and 24 weeks of interferon alpha 2a or b and ribavirin or faldaprevir 120 mg for 12 weeks and pegylated interferon alpha 2a and ribavirin for 24 weeks (or 48 weeks under response-guided rules).

Recommendation: HCV genotype 1a or 1b treatment-experienced patients should be treated with either simeprevir for 12 weeks plus 24 or 48 weeks (according to RGT rules) of interferon and ribavirin, especially if they relapsed on previous treatment or be treated with 12 weeks of interferon alpha 2 a or b, with ribavirin and sofosbuvir

Recommendation: HCV genotype 1a or b with cirrhosis or severe fibrosis should be treated with 12 weeks of interferon alpha 2a or b, with ribavirin and sofosbuvir.

Recommendation: HCV genotype 2-naïve patients should be treated with 12 weeks of ribavirin and sofosbuvir

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Recommendation: HCV genotype 2 with cirrhosis or severe fibrosis could be treated with 12 weeks of ribavirin and sofosbuvir.

Recommendation: HCV genotype 3-naïve patients could be treated with either 12 weeks of pegylated interferon and ribavirin and sofosbuvir or could be treated with 24 weeks of pegylated interferon and ribavirin or 24 weeks of sofosbuvir and ribavirin.

Recommendation: HCV genotype 3 treatment-experienced patients could be offered 24 weeks of sofosbuvir and ribavirin or 12 weeks of pegylated interferon and ribavirin and sofosbuvir.

Recommendation: Patients with cirrhosis or severe fibrosis HCV genotype 3 could be offered 24 weeks of sofosbuvir and ribavirin or 12 weeks with sofosbuvir and ribavirin and Interferon alpha, with similar efficacy

Recommendation: On an individual basis, in experienced centres, HCV genotype 4, 5 or 6 with cirrhosis or severe fibrosis could be treated with 12 weeks of interferon alpha 2a or 2b, with ribavirin and sofosbuvir

2. European Association for Study of the Liver: Recommendations on Treatment of Hepatitis C: April 2014
See attached summary - but essentially, is now out of date (PublishedApril 2014).
http://www.easl.eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014

3. American Association for Study of Liver with ID association of US: Published December 2014 and an update made in Feb 2015
http://www.hcvguidelines.org/full-report/initial-treatment-box-summary-recommendations-patients-who-are-initiating-therapy-hcv

Methodology: High quality systematic review of evidence

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1a infection (listed in alphabetic order; see text).

a) Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1a infection.
*See text for further detail on length of treatment. Rating: Class I, Level A

b) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection. Rating: Class I, Level A

c) Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24

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weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.Rating: Class IIa, Level B

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1b infection (listed in alphabetic order; see text).

a) Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1b infection.
*See text for further detail on length of treatment. Rating: Class I, Level A

b) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection. Rating: Class I, Level A The addition of weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg]) is recommended in patients with cirrhosis. Rating: Class I, Level A

c) Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection. Rating: Class IIa, Level B.

Recommended regimen for treatment-naive patients with HCV genotype 3 infection.

a) Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection. Rating: Class I, Level B

Alternative regimens for treatment-naive patients with HCV genotype 3 infection.

a) Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for IFN-eligible, treatment-naive patients with HCV genotype 3 infection Rating: Class IIa, Level A

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order; see text).

a) Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection. Rating: Class IIb, Level B

b) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection. Rating: Class I, Level B

c) Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection. Rating: Class IIa, Level B

Alternative regimens for treatment-naive patients with HCV genotype 4 infection.

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a) Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection. Rating: Class II, Level B

b) Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection. Rating: Class IIb, Level B

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? *There is little doubt that the new agents which specifically exclude PEG-Interferon will be considerably easier to use. The side-effects experienced by the patients and the impact on haematological factors are minimal compared with older therapies. It is likely that the amount (and cost) of supervision of patients on these new medications will be minimal, once we have gained more experience, and that we will need to concentrate on adherence issues more carefully.*

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
We have become used to 'stopping rules' in the use of current therapies for HCV which essentially inform the clinician that the treatment is not going to be effective, and therefore to stop treatment. However, if these new medications have cover 90% success and will clear the virus from the blood in almost all patients by 4 weeks or earlier - so it is unlikely that stopping rules as we currently use them will be relevant. It is likely that some drugs may require testing for polymorphisms (eg NS3 Q80K polymorphism with Simeprevir) and the rare relapser or non-responder may require resistance mapping, but this will be rare. In addition, clinicians will ned to be more aware of potential drug-drug interactions when using these new technologies.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? *The use of the technology in the trial closely follows current clinical practice. The most important outcomes of the trials are efficacy (SVR12), side-effect profile (and patient acceptability).*

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

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life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
First generation DAA's had significant dermatological side-effects. These medications are easier to take and are not restricted by co-administration of fat with the pills. Side-effect profiles are considerably less severe than seen with Interferon, Ribavirin and the first generation DAA's. Cannot comment on subsequent adverse effects.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; **No**
- Could lead to recommendations that 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; **No**
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities **No**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The early Access Programme in UK enabled patients access to some of the new technologies. No data available, formally, as yet.

Implementation issues

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The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Care delivery should be much easier with these new technologies. No dditional education necessary for staff.