Clinical Expert Statement Template

Thank you for agreeing to give us a personal 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. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the place of the technology in current practice?

How is the condition currently treated in the NHS?

Chronic hepatitis B is treated with either standard, or pegylated interferon, or with lamivudine, or lamivudine in combination with adefovir, or with adefovir. Newer drugs include entecavir or telbivudine, and on the horizon, tenofovir.

Is there significant geographical variation in current practice?

Yes.

Are there differences in 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?

Yes; there are differences regarding for example the indications for treatment, the need for liver biopsy, the appropriate first-line therapeutic approach, the need for combination therapy in all patients, including those with lower levels of hepatitis B replication and the possibility of using an add-on therapeutic approaches.

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?

Yes; patients with higher levels of replication may be at greater risk of developing resistance to a lineage of drugs. Patients with cirrhosis require more rapid intervention and careful monitoring. Patients with decompensated cirrhosis are not suitable for interferon treatment.

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)?

By and large these treatments are applied in specialist clinics. Specialist nurses are increasingly involved in the management of patients with chronic hepatitis B. It is mandatory to utilise specialist nurses for the management of patients on interferon.

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?

There is some variation in the application of these treatments, either as single agents or in combination. There is also some variation in the ability to prescribe newer agents which have not yet been assessed by NICE

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.

Guidelines have been published by the European Association for the study of the liver, the American Association for the study of the liver, the German Association for the study of the liver and the Asian Pacific Association for the study of the liver. Other clinical reviews have also been published which provide information.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. 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?

The circumstances in which the trials were conducted do pertain to current UK practice.

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?

Probably, the most important outcome is rapid HBV DNA suppression as this can lead to loss of HBeAg in HBeAg positive patients and is less likely to lead to resistance. The majority of patients will require long-term suppression. Serum aminotransferases usually improve once HBV DNA has been suppressed, and hepatic histology improves.

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 life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side-effect profile of new nucleoside therapies including entecavir and telbivudine are very different to those seen with interferon. By and large nucleoside analogues have few side-effects and are taken orally. It is possible that rare patients on telbivudine may have elevated creatinine phosphokinase (CPK) levels which can lead to myalgia or a myositis. These patients will need monitoring. A long-term post licensing monitoring program is in place to monitor the risk of carcinoma in patients taking entecavir. The major side effects of new nucleosides are flares in hepatitis as viral load decreases or increases. These are not usually problematic except in patients with cirrhosis who may decompensate.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK.
Is the technology 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 use?

The advantages of these new agents are more potent hepatitis B suppression, and if rapid DNA suppression occurs, lower rates of resistance. These agents are generally easy to use and will be acceptable by patients for that reason.

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.

This is an important question which has not yet been fully resolved it is thought that patients with active chronic hepatitis who show signs of progression should be treated. Patients who have very high levels of replication but are young and have minimal hepatitis can be monitored.

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.

There are well controlled registration clinical trials which provide this evidence. These peer reviewed papers have been published in authoritative journals.

Unfortunately the design of the some of these trials was not optimal which leaves open some questions regarding long-term suppression and rates of resistance. Treatment for one year is usually insufficient for the vast majority of HBeAg positive and HBeAg negative patients with chronic hepatitis B.

Implementation issues

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)?

Resistance testing might be required. Longitudinal monitoring of hepatitis B DNA will be a fundamental requirement of the institution of this technology.

Please note: The NHS is required by the Department of Health and 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 Welsh Assembly Government to vary this direction.
Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

There are a number of well established laboratories and clinical units that can implemented the requirements of the likely guidance.