Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's 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?

Tenofovir (TDF) is likely to be used as a first line therapy for HBeAg positive and negative patients with chronic hepatitis B. Patients who present with acute severe or fulminant hepatitis B may be candidates for anti-viral treatment, to rapidly reduce levels of viraemia. Patients with progressive chronic hepatitis B should be treated to reduce the risk of cirrhosis. Thus patients with active chronic hepatitis B, with histological necro-inflammation and fibrosis are candidates. Patients with advanced fibrosis or cirrhosis are also important candidates for treatment, as are patients prior to liver transplantation for end stage hepatitis B. Patients with recurrent hepatitis B post transplantation can be treated. Patients with extrahepatic disease due to hepatitis B, including those with polyarteritis nodosa, or with glomerulonephritis for example can be treated, with careful monitoring for renal impairment. Patients with haematological malignancies requiring immunosuppressive treatment or cytotoxic chemotherapy are at risk of reactivation of hepatitis B and should be given appropriate antiviral prophylaxis.

Treatment varies as the trial data are not conclusive about long-term outcomes nor on who should be treated. Lamivudine is commonly used, entecavir is increasingly used

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?

Patients with evidence of decompensated cirrhosis have a worse prognosis than patients with low levels of replication of hepatitis B who do not have active histological hepatitis or fibrosis. As stated above immunosuppressed patients may reactivate hepatitis B and develop severe or even fulminant hepatitis. Patients who have pre-existing renal impairment may be at small risk of nephrotoxicity from tenofovir and appropriate monitoring of renal function is required in all patients. The dose of tenofovir should be adjusted in line with renal function as this nucleoside analogue is cleared by the kidneys. Decreases in bone mineral density have rarely been reported in HIV positive patients treated with tenofovir.

Patients with dual infections; either HIV and HBV or HCV and HBV infections, do worse and results of trials of treating these groups for HBV infection are not available

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 in specialist clinics. Specialist nursing input will be required. Virological services to monitor HBV DNA will be required for treated patients, and to determine the indications for treatment.

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?

Tenofovir has been widely used to date as Truvada i.e. a combination of emtricitabine and tenofovir for patients with hepatitis B and HIV coinfection. Tenofovir is a very widely used agent for the treatment of HIV infection.

It is not always used as licensed; for example, it is often used in combination with other antiretroviral drugs to treat both HIV and HBV in the same patients

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.

The recently published European Association for the Study of the Liver guidelines give a clear indication for the use of tenofovir. This document provides guidelines for the indications for treatment; patients with chronic hepatitis B can be treated with either pegylated interferon or nucleoside analogues. The EASL guidelines state that the most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir should be used as first line monotherapies. It is optimal to maintain HBV DNA suppression to undetectable HBV DNA by real-time PCR. The long-term effects of safety and tolerability of entecavir and tenofovir (i.e. after five to 10 years) are still unknown.

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?

The data from phase 3 trials support an advantage of tenofovir over adefovir. The drug is a far more consistent and potent suppressor of hepatitis B replication than adefovir. Levels of suppression in both HBeAg positive and anti-HBe positive patients are similar to those observed with other newer potent nucleosides such as entecavir although these two drugs have not been compared in head-to-head comparisons. Tenofovir is a more potent inhibitor of hepatitis B replication than lamivudine. The agent will also be a more useful agent than adefovir for the treatment of lamivudine resistance. Tenofovir has proven useful for the

management of delayed or suboptimal responses to adefovir. A rapid switch to tenofovir or entecavir for these patients is recommended. In cases of resistance an appropriate rescue therapy should be initiated with the most effective antiviral agent to minimise the development of multiple drug-resistant strains. Tenofovir it is effective against lamivudine resistant strains of hepatitis B as well as the A181T/a strain of adefovir resistant hepatitis B. Tenofovir shows intermediate activity against the N236T variant associated with adefovir resistance and is effective against entecavir resistant hepatitis B.

This could improve the treatment of HBV and would be easier, and probably cheaper, than interferon-based treatment. It should be used in combination with other nucleoside analogues to prevent resistance emerging.

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.

Routine HBV DNA measurement will be required but this test is available from specialist virological laboratories. Tests for genotypic resistance will become important if resistance is shown to occur with tenofovir treatment. Appropriate testing for prior lamivudine adefovir and entecavir resistance will be required in previously treated patients.

Combination therapy should be the norm. Tenofovir can cause renal dysfunction so close renal monitoring, including phosphate levels, should be including as part of routine care. Patients should be routinely screened for HIV so that the risk of generating tenofovir-resistant HIV mutants is minimised.

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 result of the phase 3 studies are entirely applicable to patients in the UK and can be extrapolated without difficulty to patient populations in the UK. There are no known differences in outcome between different hepatitis B genotypes.

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?

Renal function particularly in patients with advanced liver disease, and bone density in patients with cirrhosis will require regular monitoring.

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.

Several investigator initiated collaborative studies have been presented in abstract form at the American Association for the study of the Liver Disease meeting as well as the European Association for The Study of the Liver over the past year

Implementation issues

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)?

In the absence of screening and increased case identification for hepatitis B, no extra resources will be required. However improved treatments for chronic hepatitis B should mean that community screening in minority groups known to be at high risk of hepatitis B, with unidentified disease, should be initiated.