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?
Three doses of intravenous Infliximab (weeks 0, 2 & 6) are given for severe systemic crohn's disease unresponsive to conventional immuno suppression and in whom surgery is inappropriate.
Similar dosing regimen for fistulising perianal disease or entero-cutaneous fistulae.
Responders are offered maintenance (8 weekly) treatment.

Is there significant geographical variation in current practice? Not that I am aware. There is a problem where certain PCTs will not grant funding which seems to be most difficult in district general hospitals where paediatricians with a special interest in gastroenterology are treating small numbers. Whether this is causally related is unclear. It may simply reflect different PCTs reluctance to grant funding.

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?
Generally not. There are no alternatives currently since monoclonal antibodies to α4 integren, (endothelial adhesion molecule) 'Natalizumab' have been withdrawn.

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 same experience as adults – more risk of hypersensitivity if long intervals between infusions. Concurrent immunosuppressives may reduce antibody formation and increase time before patient becomes refractory to the antibody. Increased risks of infections while on TNF antibodies especially tuberculosis (TB). It is recommended that TB status should be checked before giving Infliximab to a patient. There is a suggestion in the literature that treating children early rather than late in their disease may produce a better response.

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 secondary rather than a primary care usually with patients attending as a daycase. Its use in paediatrics should probably be confined to paediatric gastroenterologists with experience of using the antibody. Therefore this would usually be at the tertiary centre or if not, at another hospital which should be part of a managed clinical network (MCN) with a tertiary paediatric gastroenterology centre so there can be input from a paediatric gastroenterologist. Monitoring of the patient during and 2hrs after the infusion is necessary and is usually provided by nurses with doctors available should adverse reactions occur.

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?
Until the European license was granted in 2007, all use in UK was 'off-license' for children with IBD. Subsequently as per license in Europe.

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 of management of paediatric IBD are to be launched on website of British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN) in April 2008. These have been produced by IBD working gp (sub group of BSPGHAN). These were informed by the evidence based review completed by this same working gp on behalf of BSPGHAN. This reviewed all papers up to and including Dec 2006 containing paediatric data regarding management of paediatric IBD using SIGN (Scottish Intercollegiate Guidelines Network) methodology. Also included in this are comments from BSG (British Society of Gastroenterology) & ECCO (European Crohn's and Colitis Organisation) consensus guidelines on management of IBD in adult patients. This is the only methodological review of all paediatric data involving studies investigating management of childhood IBD using recognised, tested & validated methodology.

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?

Use in clinical setting reflects that seen in trial conditions. However, the only prospective study so far to investigate maintenance therapy for children with CD was a comparative study of the effectiveness of 8 versus 12 weekly maintenance in which 8 weekly therapy was shown to be more effective.

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?
Disease activity and quality of life scores (QOLIs) are the most important measures of success with treatment. Activity indices were used in the trials but QOLIs were not. The latter should be measured. Also none of the trials to date have been long enough to accurately record adverse events. This would be best achieved by mandatory registration of all patients receiving these antibodies.

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?

Hypersensitivity reactions are relatively common but in most have not necessitated cessation of treatment.
The most serious adverse event that did not become apparent in clinical trials has been the occurrence of hepatosplenic non-Hodgkin T- cell lymphoma. Again, as more biologicals are becoming available with different adverse effects, it becomes even more urgent that a compulsory register for use of biologics for CD is established so that any serious potential adverse effects are picked up as soon as possible and reliable prospective data on efficacy can be established. No centre should be allowed to administer biologics unless registration is done.

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?
There are not comparable alternatives available for this technology. Generally patients find hospital attendance for the infusion of the monoclonal antibody acceptable and not much more time consuming than regular outpatient reviews. If the antibody can be given by subcutaneous injection, then self administration at home is achievable. This group of patients would need their usual outpatient review at the hospital. There are generally no more tests required when receiving biologics than would usually be done during routine monitoring of the patients' CD.

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.
Infliximab is generally considered for a patient with confirmed CD who continues to relapse after several courses of primary therapy ie steroids or liquid diet therapy and who is established on immunosuppressives eg azathiaprine, 6-mercaptopurine or Methotrexate. This applies to systemic CD or fistulising disease.
There are no formal rules about stopping therapy. Many children in the UK with Crohn's have received maintenance therapy for some years. Now it is apparent that a small minority receiving Infliximab and concomitant azathiaprine or 6-mercaptopurine, have developed a hepatosplenic T-cell lymphoma, we are very aware that consideration has to be made with individual patients if they no longer need biologics. As a rule, if a patient has no breakthrough symptoms before the next 8 weekly infusion of Infliximab is due and had been like this for a year, we would recommend repeat colonoscopy to assess/confirm mucosal healing. If mucosal healing is confirmed, we would recommend withdrawal of Infliximab if the patient and their family agree.

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 guidelines and evidence based review produced by the IBD working group of BSPGHAN would be such a body of information (vide supra **clinical guidelines**)

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)?

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.

I think the structure required for administering this technology is in place other than two aspects already discussed.

1. In the paediatric setting it is important that all paediatricans using this technology are either in the tertiary centre providing tertiary paediatric gastroenterology or in a district general hospital which is part of a MCN with their tertiary provider of paediatric gastroenterology services. In this way, paediatricians with a special interest in paediatric gastroenterology may continue to supervise the provision of this technology in their own hospitals but within the framework of an MCN to ensure good clinical governance.

2. All patients given biologics must be prospectively registered onto a national (UK-based) register to detect all possible adverse events and to permit proper monitoring. There should be mandatory registration (hopefully via on on-line facility that is easy to use) BEFORE the patient receives their first dose to ensure it is not omitted.