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?

Crohn's disease is a chronic relapsing inflammatory disease with considerable morbidity. Upto 80% of patients may undergo surgery over a 25 year follow-up period in population based studies, suggesting that only a minority of patients have a benign course of disease. Duration of disease also correlates with complications such as development of fistulae and strictures which may lead to surgery including mutilating surgery such as permanent ileostomy. Early intervention with immunomodulator drugs and anti-TNF therapy may reduce relapses and heal the mucosa (Hommes D *et al* Lancet 2008 in press).

Disease severity may be difficult to assess in Crohn's disease and is not dictated by CDAI alone, but also previous therapeutic history and/or surgical interventions. Complex perianal fistulising Crohn's disease is often clinically regarded as severe disease irrespective of CDAI, due to considerable requirement for surgical interventions and hospitalisations.

Corticosteroid therapy does not heal the mucosa and has little maintenance value. It is used as induction therapy, but 20% of patients fail therapy and approximately 40% become steroid dependent with formidable side effects such as osteopenia, moon face, diabetes, mood disturbances, infections and poor surgical outcomes. It is now recommended for use only for short periods (approximately 12 weeks in tapering dose). In mild disease, budesonide or defined formula diet (mainly in paediatric disease) is used as induction therapy, but efficacy is lower than conventional steroids.

In patients who fail to respond to steroids, become steroid dependent or require frequent steroids (twice a year or thrice in two years) are treated with immunomodulator drugs (azathioprine, 6-mercaptopurine or methotrexate). Increasingly, such immunomodulator drugs are used early in an attempt to maintain remission as shown in paediatric Crohn's disease trials (Markowitz *et al* Gastroenterology 2000).

In patients intolerant of (upto 20-30%) or failing immunomodulator drugs (upto 40%) anti-TNF therapy or surgery are considered. It has been established that patients prefer medical therapy before agreeing to surgery and often surgery can be mutilating (colectomy), not feasible (extensive resections) or an adjunctive therapy to medical therapy (draining perianal abscess). These patients are often severely ill despite their CDAI often being lower than 300.

In patients who are very symptomatic (ie CDAI >300) and failed steroid therapy, immunomodulator therapy is inappropriate as monotherapy as it is too slow and in this situation, anti-TNF therapy is very useful clinically to induce rapid remission in responders. Bridging to immunomodulator is acceptable but not optimal in this situation.

The above view is consistent with European consensus published in 2006 (Gut) and should replace older national guidelines.

With over 9 years of use of infliximab it is clear that regular maintenance therapy given every 8 weeks is the optimum therapy accepted by most experts and the standard way of administration in USA, Canada and most of Western Europe (Scandinavia, Netherlands, France, Belgium, Spain and Italy). Intermittent use is immunogenic, results in higher infusion reactions and delayed hypersensitivity and eventual loss of response. This is especially true in patients not on immunomodulators. In my

experience, intermittent therapy on relapse is extremely unsatisfactory and patients should never be allowed to relapse severely to earn therapy- such therapy loses response rapidly and often results in delayed hypersensitivity. Adalimumab has never been used in a trial as intermittent therapy. In my opinion, intermittent therapy with anti-TNF can no longer be considered acceptable standard of therapy.

Approximately 20% of patients would lose response in a year, but it is clear now (Leuven data 2007) that this loss of response is not cumulative and upto 70% of patients will be retained on the drug long-term. Loss of response may be treated by increase in dose, decrease in interval or switching to another anti-TNF (GAIN).

Whether anti-TNF therapy should be routinely combined with immunomodulator therapy is currently under debate. Monotherapy may result in higher immunogenicity. Hepatosplenic T cell lymphoma in young patients (11 Crohn's; 2 ulcerative colitis) is rare and no new case has been reported in the last 16 months. Studies in progress (SONIC, COMMIT) will address this question, but in the interim, combination therapy may be considered optimum from the standpoint of efficacy, though monotherapy with anti-TNF is also acceptable. A small randomised control trial (Van Assche et al 2007) of withdrawal of immunomodulator from anti-TNF maintained patients compared with combination therapy (40 patients in each arm) showed no difference in efficacy, but was grossly underpowered and showed increased immunogenicity in the monotherapy arm. In Canadian paediatric patients where immunomodulator therapy was withdrawn from a large number of patients on anti-TNF, a drop in response rate was seen (Dr Ann Griffiths, personal communication).

Infliximab and adalimumab are similar in efficacy and safety, but different in mode of administration and frequency of administration.

Is there significant geographical variation in current practice?

There is significant variation in UK, but European ECCO expert consensus is now well accepted in clinical practice (Gut 2006). Variation in UK practice is mainly centred around current (but outdated) NIHCE guidelines recommending episodic therapy on severe relapse, but a move in clinical practice clearly towards maintenance therapy in a scheduled manner. This results in variation in access depending on PCT commissioners interpretation of current evidence.

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?

In Europe a consensus amongst ECCO experts has been reached regarding current practice, and this is widely accepted in Europe. Almost all experts now agree that maintenance therapy with anti-TNF is optimal use and intermittent therapy is discarded.

Experts also agree that treating only relapses without a strategy to maintain remission is not ideal treatment for Crohn's disease, and similar to rheumatoid arthritis, disease modification and long-term therapy has become widely accepted practice in most Western European countries (as well as Hungary, Poland and Czech Republic).

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?

Complex perianal fistulising Crohn's disease patients have a poor outcome and respond poorly to conventional therapy. These patients require aggressive therapy early with anti-TNF agents combined with surgical drainage. Steroid dependent patients are at considerable risk of steroid side effects and aggressive therapy with immunomodulator drugs and/or anti-TNF is required to wean these patients off steroid therapy. These patients should really be considered in the severe category irrespective of their CDAI and the Lemann *et al* Gastroenterology 2006 GETAID trial is therefore a very important piece of evidence.

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)?

Both infliximab and adalimumab should be prescribed in a hospital setting by gastroenterologists familiar with the management of inflammatory bowel disease. Infliximab is administered intravenously and therefore would require nursing support for supervision of the infusion. Adalimumab may be self administered at home. Even in patients who have responded well, follow up every 3-4 months by a gastroenterologist is recommended.

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 variation in the use of infliximab within the NHS regarding episodic versus scheduled maintenance treatment with infliximab and in the duration of use of the drug. Use of adalimumab is also variable as it is currently not covered by NIHSE guidelines. Usually it is used within the licensed indications after failure of conventional therapy, but severity of disease is generally not judged just on the basis of CDAI. Indeed CDAI is uncommonly used within the clinical setting. Adalimumab is also used for fistulising Crohn's disease despite lack of specific indication and both drugs are used for unclassified colitis (no definite distinction possible between ulcerative colitis and Crohn's disease). A lot of variation in practice is due to the variable degree of application of CDAI criteria (not an appropriate selection tool in clinical practice in isolation).

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 European Crohn's and Colitis Organisation (ECCO) has published consensus based guidelines (Gut 2006), using systematic review of the literature and underpinning consensus statements by evidence level and recommendation grade. The AGA consensus published in Gastroenterology 2007 used a similar evidence based consensus approach.

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 of CDAI alone in clinical practice as opposed to clinical trials in order to select severe patients is problematic. In practice other factors are considered, such as previous failed therapy, previous surgery, patient preference, presence of adverse disease features (complex perianal Crohn's disease) and availability of acceptable surgical options (ileal resection often more acceptable to patients than a total colectomy).

In clinical trials strict definition of therapy failure is used, so that any minor escalation of steroid dose would count as therapy failure, but this is not so in practice. Therefore recent experience of centres (Leuven, Belgium) with high use of infliximab show results that are better than clinical trials (Ferrante et al 2007).

In ACCENT I trial (infliximab), responders (70 point CDAI drop + 25% decrease) at week 2 were randomised to placebo or active treatment. In CHARM trial (adalimumab), responders (70 point CDAI drop) at week 4 were randomised to placebo or active treatment. In clinical practice, responders after at least 6-12 weeks will be continued on therapy and therefore responder numbers are higher. It is important to note much higher remission rates in some clinical trials (Lemann et al 2006, Hommes et al 2008) after infliximab induction, illustrating the value of earlier therapy. Patients with shorter duration of disease even after failing steroids and immunomodulators have better response rates than those with longer duration of disease.

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 cost of managing Crohn's disease is dominated by hospitalisation and surgery and reduction of hospitalisation rates and surgical rates are important outcome measures. Both were measured in fistulising (ACCENT II) and non-fistulising disease (ACCENT I) treated with infliximab or placebo and reported. Hospitalisation rates have been reported in CHARM trial (adalimumab) and surgical rates were measured but not reported yet.

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 most important adverse events are serious infections and opportunistic infections. Tuberculosis rates have declined after introduction of rigorous screening (approx 0.5/1000). Other opportunistic infections (including viral) are important but rare. Patients with hepatitis B may worsen and Herpes may flare up. Both an European (ENCORE) and an US (TREAT) registry are monitoring these and other side effects. Such registries are important sources of post-marketing adverse event data. The adverse event appears comparable to immunomodulators but steroids are worse for increasing susceptibility to infections.

There is no clear evidence that anti-TNF drugs increase malignancy rate or lymphoma rate. The rare occurrence of hepatosplenic T cell lymphoma in young patients exposed to infliximab and azathioprine was described in the post-marketing phase but FDA approved license after evaluating this data. No new case has been reported in the last 16 months (11 HSTCL in Crohn's; 2 in Ulcerative colitis – approximately 90,000 young patients exposed to infliximab). 2 cases have been reported in patients exposed to azathioprine alone.

Serious treatment related infusion reactions are rare (<1%), but more common with episodic therapy. Adalimumab pen device is better tolerated than the syringe device used in trials in terms of injection site pain. Delayed hypersensitivity reaction is rare with scheduled administration.

Other side effects are very rare, including demyelination, abnormal liver function tests and skin rashes. Surgical risks or postoperative complications are not increased by pre-operative use of anti-TNF therapy.

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?

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 has been in use for Crohn's disease for over 9 years and is now considered part of mainstream therapy for refractory Crohn's disease. For patients failing steroid and immunomodulatory therapy in Crohn's disease and where no easily acceptable surgical alternative therapy is available, there are no alternatives available for use. Approximately 10% of patients will fall in this category, though in Western Europe up to 15% of patients are now receiving anti-TNF therapy.

There is considerable familiarity in the use of anti-TNF therapy in most large GI units and patient acceptability is high due to rapidity of onset of action. Availability of subcutaneous pen device will permit even easier, domiciliary administration.

Formal rule for starting therapy is embodied in the ECCO consensus document. No formal stopping rules are available. It is clear that anti-TNF therapy may be stopped in a proportion of patients (Leuven data). This may include immunomodulator naïve patients with severe disease started on anti-TNF (immunomodulator being too slow) and then bridged to immunomodulator after remission. Infliximab has license for such 2nd line use.

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.

Critical studies that will influence practice are in progress including SONIC and COMMIT (infliximab) and PARADIGM (adalimumab). In addition, trial of a stop strategy based on remission induced by infliximab and mucosal healing is in progress by GETAID group in France. All these studies will provide pivotal evidence during 2009-2010. SONIC and COMMIT have concluded recruitment.

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.

No additional resources are likely as infliximab is widely in use; if anything availability of adalimumab may simplify administration by permitting self-administration. However intermittent therapy still in use in some centres is unlikely to be an acceptable form of therapy, and if maintenance therapy is approved by NIHCE, some additional resources (nursing time) may be required.