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.

About you

Your name: [redacted]

Name of your organisation: Royal College of Physicians

Response coordinated by [redacted] **and** [redacted] **the** [redacted]

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)? Yes
- people with the condition for which NICE is considering this technology?
- 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.)?
- other? (please specify)

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?

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?

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)?

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?

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.

1. In-patients with acute severe UC are conventionally treated initially with intravenous hydrocortisone or methyl prednisolone. If they fail to respond within 3-5 days, the alternative treatment options are infliximab, ciclosporine or surgery. It is important to note that "severe" in this context is quite precisely defined, usually using the Truelove and Witts criteria that include 6 or more bloody stools per day, and one or more of fever (>37.5 degrees C), tachycardia (>90/min), anaemia (haemoglobin <10 g/dl), or hypoalbuminaemia (<35 g/dl). It used to be associated with a mortality of over 25% in the pre-corticosteroid era and is still associated with a mortality of about 1-1.5% (see later). It is therefore universally accepted that severe colitis as so defined is an indication for emergency admission to hospital, treatment with intravenous corticosteroids, and careful monitoring. Approximately between one in three and one in five patients with severe colitis require colectomy during the admission. This requirement for colectomy is probably reduced by about 50% in the short term, perhaps 25% in the long term, by the use of ciclosporin or infliximab in patients who are not showing a rapid response to corticosteroids.

We are not aware of major *geographical* differences in current practice although suspect that in DGHs use of ciclosporine (because of difficulties in monitoring blood levels) and of infliximab (because of difficulties in funding and lack of experience) are used less than in tertiary centres. In the recent UK IBD Audit 2006 (see below), 28% patients with acute severe UC responded well to iv steroids; in the remainder with steroid-refractory disease, the treatments used were surgery in 42% cases, ciclosporine in 28% and infliximab in 4%

Intravenous ciclosporine (4 mg/kg) has been used for steroid-refractory acute severe UC for about 12 years (Lichtiger S, New Eng J Med 1994;330:1841-51) with a response rate, measured by avoidance of colectomy, of about 70% acutely; up to 60% of patients 'rescued' with ciclosporine, however, come to colectomy within a year of this episode (Arts J, Inflamm Bowel Dis 2004;10:73-8, and several other large series). Ciclosporine at this dose is associated with several serious side effects including opportunistic infection, neuropsychiatric disturbances including fits, renal

malfunction, hypertension, electrolyte disturbances and drug interactions; these side effects are more common in older people but have been associated in large series with a mortality (mainly due to infection) of about 3% (Arts 2004). More recently, the side effect profile of ciclosporine has been improved by using a lower dose (2 mg/kg) intravenously, or initiating therapy orally – the evidence base for the efficacy of these approaches is less firm than for 4 mg/kg intravenously and we are aware that the Leuven group, who have pioneered the use of low dose ciclosporin, are themselves routinely using infliximab in preference to low dose ciclosporin this setting because of perceived greater safety (Prof Rutgeerts, personal communication). The only other accepted alternative therapy in steroid-refractory acute severe UC is urgent sub-total colectomy with ileostomy and, in most patients, subsequent formation of an ileoanal pouch anastomosis. Surgery of this sort itself carries a small but finite risk of mortality, particularly in the setting of acute severe colitis (1% in specialist centres, up to 20% in non-specialist units, 2% according to the UK IBD Audit 2006 (which may not have produced randomly representative data)), as well as long term sequelae including diarrhoea, faecal incontinence, pouchitis and sexual dysfunction including impairment of fertility. The effects of such surgery on quality of life are variable (Lichtenstein G, J Clin Gastro 2006;40:669-77).

2. In acute severe steroid-refractory UC, it could be argued that a treatment which avoids surgery (e.g. infliximab or ciclosporine) is of even greater benefit in patients presenting for the first time as emergency admissions with acute severe UC than in those who have had the disease for a long period with or without several admissions for treatment of severe relapses (see also below). At any time, surgery has a major psychological impact on patients, but this is even more marked in those who have had little or no time to come to terms with their disease, and with the idea that surgery with ileostomy and subsequent pouch formation is necessary. These patients will of course have had no prior therapy and in particular will not have had time to gain benefit from immunosupressives such as azathioprine.

Many patients are aware of the disadvantages of surgery in relation both to the risks of the operation itself and its long term sequelae (see above) and specifically request alternatives such as infliximab if they prove refractory to, or intolerant of the drugs listed under 1. above. Older patients, however, appear to be at greater risk of fatal complications (particularly infection) of use of infliximab (Colombel JF, Gastroenterology 2004;126:19-31) and in such patients colectomy might be a safer option.

3. Infliximab in steroid-refractory acute severe UC would be used always in hospital wards in secondary care during in-patient admission.

4. The UK IBD Audit 2006 indicates that use of infliximab in steroid-refractory acute severe in-patient UC at present is rare (see above). We do not know whether this is due to patient and clinician preference but suspect that it may be due to lack of NICE approval for this indication.

5. Relevant guidelines include those produced by the European Colitis and Crohn's Organisation (ECCO) (in press) and by the American Gastroenterological Association (Gastroenterology 2006;130:940-987). These guidelines were drawn up following exhaustive reviews of the literature followed by an iterative process of consultation between acknowledged experts in IBD in Europe and the USA respectively; the quality of evidence on which recommendations were based was meticulously graded. The principal evidence supporting use of infliximab in steroid-refractory acute severe inpatient UC comes from the trial by Jarnerot (Gastroenterology 2005;128:1805-1811), which showed that a single infusion of infliximab 5 mg/kg was associated with

a colectomy rate of 30% after three months, in comparison with nearly 70% in patients treated with placebo; in this study infliximab was less effective in fulminant UC than in less severe acute attacks. The benefit in preventing colectomy was sustained out to 2 years (presented DDW 2007). A discordant note was provided by Probert et al (Gut 2003;52:998-1002), who reported that infliximab 5 mg/kg at weeks 0 and 2 in in-patients with steroid-refractory acute severe UC was no better than placebo in inducing clinical remission (39% versus 30% respectively) or sigmoidoscopic remission (26% versus 30%).

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?

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.

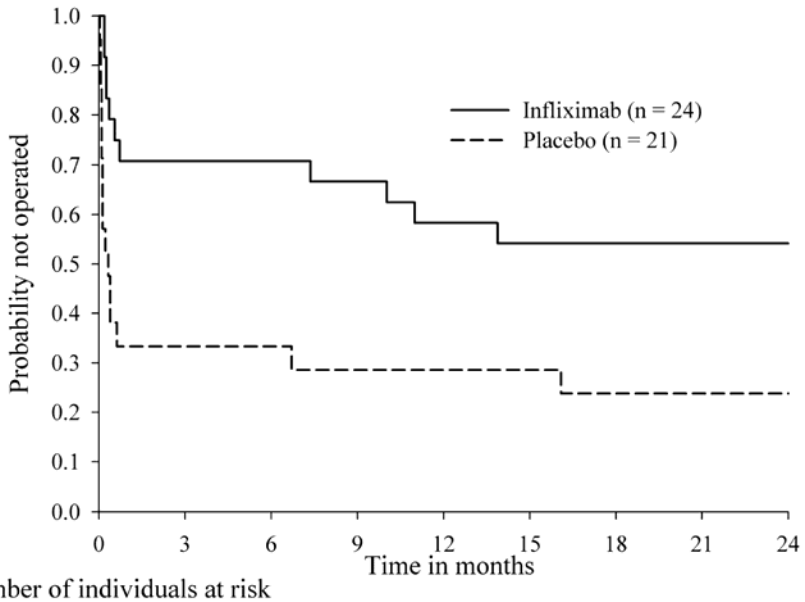
If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the 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?

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?

1. In patients given a single infusion of infliximab for acute severe steroid-refractory inpatient UC, azathioprine is usually started concurrently to try to maintain subsequent remission in infliximab-responders.

2. In acute severe steroid-refractory inpatient UC, we recommend that a single infusion of infliximab 5mg/kg should be given at day 3 of iv hydrocortisone treatment in patients with CRP.45 or >8 stools/day (the 'Travis' criteria indicating an 85% chance of non-response to steroids)(Travis S, Gut 1996;38:905-10). The alternative would be ciclosporine (see above). In each case, azathioprine or mercaptopurine should be started before hospital discharge to optimise subsequent maintenance of remission. It can be argued that infliximab (and ciclosporine) should be considered only in patients presenting to hospital with UC for the first time, or in those normally maintained on a 5ASA alone, since if a patient has severe UC despite treatment with an immunomodulator, there is little chance of long-term medically maintained remission, and prompt surgery for steroid-refractory patients is the best option (ECCO Guidelines; 2007)

3. The best trial in acute severe steroid-refractory inpatient UC is Jarnerot's (Gastroenterology 2005;128:1805-1812). The end-point (colectomy rate at 3 months) is unexceptionable; there were no deaths and subsequent 2 year follow-up shows maintained benefit (Gustavsson et al, Gastroenterology 2007 132:A146 – see figure:



Number of individuals at risk

Infliximab	24	17	17	14	13
Placebo	21	7	7	6	5

The disease activity scores used are not widely employed in the UK, where the Travis score at 3 days is favoured (see above). Otherwise the trial is representative of UK practice.

4. In UC, the side-effects of infliximab are likely to be the same as they are in Crohn's (infusion reactions, infections, neoplasia including lymphoma, demyelination, heart failure etc). There appears to be no increase in surgical complications in patients needing an operation because of failure to respond to infliximab. There is an approximately 1% drug-associated mortality in patients given a mean of 4 infusions for Crohn's disease over a year (Colombel, Gastroenterology 2004;126:19-31)

In the Jarnerot study (Gastroenterology 2005) involving a single infusion of infliximab in steroid-refractory acute severe inpatient UC, there were no major complications. It is possible, though not we think formally proven, that a single infusion of infliximab will be associated with fewer side-effects than a series of such treatments (Colombel 2004).

In inpatient steroid-refractory acute severe UC, the alternatives to infliximab are ciclosporine and urgent surgery. As already indicated, ciclosporine has a wide spectrum of side-effects, and carries a 3% risk of drug-associated mortality if given iv at 4mg/kg (Arts 2004). Urgent surgery carries a high risk of morbidity and mortality (see above); its long-term adverse sequelae are also substantial, making a single infusion of infliximab an attractive alternative to these two options in this setting.

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.

Other sources of information include:

i. The recently completed National UK IBD Audit 2006 (sponsored by British Society of Gastroenterology, Royal College of Physicians, Association of Coloproctologists of Great Britain and Ireland, and National Association for Colitis and Crohn's disease, to the organisation of which one of these reviewers (JMR) has made a major contribution. This gives data on current treatment of acute severe inpatient UC in the UK, including the use of infliximab, ciclosporine and surgery, and the outcome of such treatment, including mortality.
ii. Under the auspices of the Health Technology Agency, a nationwide UK clinical trial has been designed by Prof CJ Hawkey (Queens Medical Centre, Nottingham) to compare the efficacy and safety of infliximab and ciclosporine in the treatment of acute severe UC. This trial is unlikely to achieve publication for 4-5 years.
iii. Records of side-effects attributable to infliximab (at least in relation to Crohn's) are provided by the commercially sponsored European ENCORE registry and the older and larger US TREAT registry (Lichtenstein GR, Clin Gastro Hepatol 2006;4:621-30). A further European registry (OUTLOOK) to study use of infliximab in UC has recently been established.

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)?

Infliximab is already widely used in patients with otherwise refractory Crohn's disease (as well as in rheumatology – see above). Specialist NHS staff (medical and nursing) already supervise and administer use of infliximab in Crohn's and would be the same staff who administer the treatment in UC: no additional education, training, facilities or equipment would be needed.