

## The management of steroid resistant ulcerative colitis

### Introduction

The aim of the HTA programme is to ensure that high quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms the largest portfolio of work in the NHS Research and Development Programme and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

### Question

*What is the clinical and cost effectiveness of adding ciclosporin or infliximab to standard therapy in patients with severe steroid resistant ulcerative colitis?*

- 1 **Technology:** Ciclosporin and infliximab.
- 2 **Patient group:** Patients with severe steroid resistant ulcerative colitis (to be defined with a scoring system chosen and justified by researchers) who do not require urgent surgery.
- 3 **Setting:** Secondary care.
- 4 **Control or comparator treatment:** Standard treatment: intravenous hydrocortisone 100mg qds, with liquid steroid enemas, and prophylactic heparin.
- 5 **Design:** A two arm randomised controlled trial. Patients all receiving standard care plus being randomised to either 1) ciclosporin or 2) infliximab. Proposals for a third arm trialling an additional biological agent will be considered, but the choice of agent should be supported by systematic review evidence.
- 6 **Primary outcomes:** Quality of Life. Other outcomes: avoidance of colectomy for one year, reduction in colectomy rate and induction of remission. The trial should be powered on the comparison between imatinib (or other biological) and ciclosporin.
- 7 **Minimum duration of follow-up:** One year.
- 8 **Is the research question concerned with a licensed or unlicensed indication for the drug in question?** Ulcerative colitis is an unlicensed indication for ciclosporin. Infliximab is licensed for management of severe active Crohn's disease (but not ulcerative colitis).

#### Background to commissioning brief:

*Ulcerative colitis is characterized by a life-long chronic course with remissions and exacerbations. The goal of therapy is to induce and maintain remission, and to improve the quality of life. The introduction of ciclosporin for use in patients with severe ulcerative colitis has provided a new medical alternative to patients previously faced with only surgical options, its effect on quality of life has not been systematically assessed and there is still controversy concerning its use.*

*Research is required in the form of a randomised controlled trial to evaluate the clinical and cost effectiveness of adding ciclosporin or infliximab to standard therapy in patients with severe steroid resistant ulcerative colitis. Primary outcome to be quality of life, instruments and measures to be specified and justified by researchers.*

## Notes to Applicants

For many of the questions posed by the HTA programme, a randomised controlled trial is likely to be the most appropriate method of providing an answer. However, there may be practical or ethical reasons why this might not be possible. Applicants proposing other research methods are invited to justify these choices.

Applicants are asked to:

1. Follow the Medical Research Council's Good Clinical Practice guidelines (<http://www.mrc.ac.uk/pdf-ctg.pdf>) when planning how studies, particularly RCTs, will be supervised. Further advice specific to each topic will be given by the HTA programme at full proposal and contract stages.
2. Note that trials involving medicinal products must comply with "The Medicines for Human Use (Clinical Trials) Regulations 2004". In the case of such trials, the DH expects the employing institution of the chief investigator to be nominated as the sponsor. Other institutions may wish to take on this responsibility or agree co-sponsorship with the employing institution. The DH is prepared to accept the nomination of multiple sponsors. Applicants who are asked to submit a full proposal will need to obtain confirmation of a sponsor(s) to complete their application. The DH reserve the right to withdraw from funding the project if they are not satisfied with the arrangements put in place to conduct the trial.

The MHRA ([info@mhra.gsi.gov.uk](mailto:info@mhra.gsi.gov.uk), <http://www.mhra.gov.uk>) can provide guidance as to whether your trial would be covered by the regulations. The DH/MRC website (<http://www.ct-toolkit.ac.uk/>) also contains the latest information about Clinical Trials regulations and a helpful FAQ page.

## Making an application

If you wish to submit an outline proposal on this topic, complete the electronic application form and return it to the HTA Commissioning Manager at the National Coordinating Centre for Health Technology Assessment, Mailpoint 728 Boldrewood, University of Southampton, Southampton SO16 7PX by **7 February 2007**. Outline applications will be considered by the HTA Commissioning Board at its meeting in **July 2007**. If they are acceptable, investigators will be given a minimum of eight weeks to submit a full proposal.

***Applications received after 1300 hours on the due date will not be considered.***

***Please see GUIDANCE ON APPLICATIONS overleaf.***

## Guidance on applications

### Required expertise

HTA is a multidisciplinary enterprise. It needs to draw on the expertise and knowledge of clinicians and of those trained in health service research methodologies such as health economics, medical statistics, study design and qualitative approaches. HTA expects applicants to engage a qualified Trial Manager for appropriate projects. Applicants will need to show a commitment to team working and may wish to consider a collaborative approach between several institutions. It is expected that the research will be undertaken only following a thorough literature review.

### Public involvement in research

The HTA programme recognises the increasing active involvement of members of the public in research and would like to support research projects appropriately. The HTA programme encourages applicants to consider *how* the scientific quality, feasibility or practicality of their proposal *might* be improved by involving members of the public. Research teams wishing to involve members of the public should include in their application: the aims of active involvement in this project; a description of the members of the public (to be) involved; a description of the methods of involvement; and an appropriate budget. Applications that involve members of the public will not, for that reason alone, be favoured over proposals that do not but it is hoped that the involvement of members of the public will improve the quality of the application.

### Outcomes

Wherever possible, the results of HTA should provide information about the effectiveness and cost-effectiveness of care provided in its usual clinical setting and for the diverse subjects who would be eligible for the interventions under study. The endpoints of interest will in most cases include disease specific measures, health related quality of life and costs (directly and indirectly related to patient management). Wherever possible, these measurements should be made by individuals who are unaware of the treatment allocation of the subjects they are assessing. We encourage applicants to involve users of health care in the preparation of their proposal, for instance in selecting patient-oriented outcomes. A period of follow up should be undertaken which is sufficient to ensure that a wider range of effects are identified other than those which are evident immediately after treatment. These factors should guide applicants in their choice of subjects, settings and measurements made.

### Sample size

A formal estimate should be made of the number of subjects required to show important differences in the chosen primary outcome measure. Justification of this estimate will be expected in the application.

### Communication

Communication of the results of research to decision makers in the NHS is central to the HTA Programme. Successful applicants will be required to submit a single final report for publication by the HTA programme. They are also required to seek peer-reviewed publication of their results elsewhere and may also be asked to support the NCCHTA in further efforts to ensure that results are readily available to all relevant parties in the NHS. Where findings demonstrate continuing uncertainty, these should be highlighted as areas for further research.

### Timescale

There are no fixed limits on the duration of projects or funding and proposals should be tailored to fully address the problem (including long-term follow-up if necessary). Applicants should consider however that there is a pressing need within the NHS for this research, and so the duration of the research needs to be timely.