Is surveillance for Barrett's Oesophagus worthwhile?

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 and work in the NHS. Questions are identified and prioritised to meet the needs of the NHS and its patients. Health technology assessment forms the largest portfolio of work in the NHS Research and Development Programme and each year about forty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include primary and secondary research and cost about £10 million a year.

Question

In people with Barrett's oesophagus or oesophageal dysplasia, is surveillance by periodic endoscopy and biopsy cost effective in terms of survival and quality of life compared to offering immediate investigation in response to changes in symptoms?

1. **Technology:** surveillance programme using endoscopy and biopsy
2. **Patient Group:** population presenting for upper GI endoscopy and diagnosed with Barrett's oesophagus excluding patients with high grade dysplasia
3. **Setting:** Outpatient-based endoscopy services
4. **Design:** primary research is required in the form of a randomised controlled trial comparing surveillance to no surveillance (researchers should specify their choice, and the exact nature, of the comparator arm).
5. **Outcomes:** The primary outcome should be survival. Other outcomes should include quality of life, incidence of oesophageal adenocarcinoma, death from oesophageal adenocarcinoma, death from other causes (specified), performance of endoscopy and biopsy as a surveillance test, including procedure-related morbidity, treatment-related morbidity, disease recurrence and quality of life, and physician and patient preferences regarding surveillance.
6. **Other issues:** Researchers need to carefully consider and demonstrate in their application how they will manage a number of pertinent issues
    a. The sample size (including whether this is to be an equivalence study or a superiority study; and the implications of this for sample size)
    b. An appropriate duration of follow-up
    c. Aspects relating to recruitment including: whether a pilot or feasibility phase would be useful; how recruitment of both professionals and patients will be achieved; any implications of the ongoing ASPECT trial, whether this will impact on recruitment and how the proposed study can link with the ASPECT trial.

Summary of research need:

Barrett's oesophagus is associated with a risk between 30 and 125 times that of the general population of developing oesophageal adenocarcinoma. Surveillance programmes are widespread throughout the UK, but vary substantially in the biopsy protocols they follow in detecting dysplastic changes and the intervals at which they review patients.

Primary research, in the form of an RCT, comparing surveillance with no surveillance, is required. The intervals for surveillance of Barrett's oesophagus and dysplastic states should be chosen to reflect current clinical practice (i.e. three to five years). Information should be collected on the time to changes between these conditions and stage at diagnosis of cancer. Quality of life should be measured using appropriate disease specific and generic, preference-based measures to facilitate cost utility analysis. Costs should be measured from the perspective of the NHS.

This research question emerged out of a report into Surveillance for Barrett's Oesophagus that the HTA programme commissioned from the Peninsula Technology Assessment Group (PenTAG) (project reference 03/49/01). The aim of this project was 'to summarise what we know and what we need to know about the value of surveillance for Barrett's oesophagus.' From more information, see the NCCHTA website (http://www.ncchta.org). The report from this project is currently being prepared for publication in the HTA monograph series; however the authors have kindly agreed to make available a pre-publication copy of their report in confidence. Applicants can obtain a copy of this report by returning a signed HTA Confidentiality Agreement (available at http://www.ncchta.org/calls/05-12.htm). Applicants should take account of this report in their application.

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 European Union Directive 2001/20/EC. For trials covered by the Directive the DH, with the HTA programme acting as their agent, is prepared, *in principle*, to be nominated as the sponsor. The responsibilities of the sponsor, as indicated by the directive, will then be agreed amongst the HTA programme, the host institution and the successful applicant. The DH reserve the right to withdraw from the role of sponsor if they are not satisfied with the arrangements put in place to conduct the trial. Experience shows that some host institutions prefer to assume the role of sponsor for purposes of the EU Clinical Trials Directive [2001/20/EC]. This is consistent with their duties and responsibilities under the Research Governance Framework and the HTA programme would support this approach.

If you are not clear as to whether your trial is covered by the directive you should contact the MHRA (info@mhra.gsi.gov.uk) for help in this matter.
Their website (http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrialdir.htm) contains the latest information about the EU Clinical Trials Directive [2001/20/EC] 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 Commissioning Manager at the National Coordinating Centre for Health Technology Assessment, Mailpoint 728 Boldrewood, University of Southampton, Southampton SO16 7PX by ***Wednesday 27 April 2005.*** Outline applications will be considered by the HTA Commissioning Board at its meeting in *July***.** 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.

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 consumers 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. However, there is a pressing need within the NHS for the information and so the research would normally be expected to be completed within three years, unless long-term follow-up is necessary.

In evaluating diagnostic and imaging techniques, the emphasis of the HTA programme is to assess the effect on patient management and outcomes (particularly where changes in management can be shown to have patient benefits). Improvements in diagnostic accuracy, whilst relevant, are not the primary interest of this commissioned research programme. Applicants should justify where they consider improvements in diagnostic accuracy to be relevant to these objectives. Where there is poor evidence to link diagnostic improvements to patient benefits, part of the primary research may be to assess the effects of such changes on patient outcome.

An assessment should also be made of changes in other resources (particularly other subsequent therapies) used as a result of changes in diagnostic methods.