Pseudomonas aeruginosa in cystic fibrosis patients

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 a substantial portfolio of work within the National Institute for Health Research 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 intravenous antibiotics after the first Pseudomonas aeruginosa culture in delaying re-infection of the lungs of cystic fibrosis sufferers?

1. **Technology:** A 10 day course of intravenous antibiotics (anti-pseudomonal agents such as ceftazidime and tobramycin.)
2. **Patient group:** Patients of any age with cystic fibrosis with a first *Pseudomonas aeruginosa* culture.
3. **Setting:** Secondary care and specialist units.
4. **Control or comparator treatment:** Oral ciprofloxacin and nebulised colomycin (Danish Protocol). This protocol is currently recommended by the Cystic Fibrosis Trust.
5. **Design:** A multicentre randomised controlled trial comparing intravenous antibiotics with oral ciprofloxacin and nebulised colomycin is required.
6. **Primary outcome:** Time to reinfection with *Pseudomonas aeruginosa.* Secondary outcomes: To include quality of life, re-admission, time to resolution of first infection, cost and cost effectiveness.
7. **Minimum duration of follow-up:** Two years.
8. **Is the research question concerned with a licensed or unlicensed indication for the drug in question?** Ceftazidime – licensed for this indication for all ages; tobramycin – licensed for this indication for all ages.

Summary of research need:

Cystic fibrosis (CF) is the UK's most common life threatening inherited disease in Caucasian populations. It is a multi system disease having particular effects on the pancreas and lungs. The primary cause of death in CF is respiratory failure resulting from chronic pulmonary infection. Pseudomonas aeruginosa (P.aeruginosa) is the most frequent cause of chronic pulmonary infection beyond infancy in people with CF. Nationally in 2003 around 10% of children grew P. aeruginosa.

Once chronic infection is established eradication is seldom achieved. It is uncertain whether eradication strategies result in increased survival or improved quality of life for patients with cystic fibrosis. Research is required to evaluate the effectiveness of anti-pseudomonal antibiotic treatment given at the time of first isolation in preventing or delaying re-infection and subsequent colonisation with mucoid strains thereby delaying or preventing lung inflammation and infection.

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, 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.

Research networks

The HTA programme expects, where appropriate, that applicants will work with the relevant research network.

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 **8 August 2007.** Outline applications will be considered by the HTA Commissioning Board at its meeting in *November 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. The HTA programme expects teams proposing randomised controlled trials to include input from an accredited clinical trials unit, or one with equivalent experience. Applicants are also expected to engage a qualified Trial Manager for appropriate projects. A commitment to team working must be shown and applicants may wish to consider a collaborative approach between several institutions

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.