A feasibility study and trial protocol development for a UK based screening programme for lung cancer utilising low dose computerised tomography

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

Researchers are asked to submit a proposal for a feasibility study that will include the development of a detailed protocol for a controlled trial with an initial pilot study to investigate the clinical and cost effectiveness of low dose spiral computerised tomography screening for lung cancer in the UK. The parameters selected for the trial should be explored and justified in detailed analyses in the feasibility study as described further in this brief. It is important that researchers should consider how a UK trial can benefit from, and add value to similar trials ongoing in other countries.

This research has three key phases described below under "The HTA Commissioning Process".

The first phase is to undertake a feasibility study to explore areas of uncertainty in the design and implementation of a controlled trial for lung cancer screening in the UK. The feasibility study should i) model important areas of uncertainty and the potential impact of selecting different values of parameters in the trial ii) describe the care pathways of subjects undergoing screening, through subsequent investigation and treatments, iii) include an analysis of benefits and harms resulting from appropriate intervention as well as from false positive and negative results, and iv) on the basis of this information should justify the parameters to be used within the controlled trial. The protocol for the trial will include an initial pilot study, the costs of both being clearly described. The pilot study may include sub studies to better refine the parameters for use in the proposed full trial. Researchers will need to provide a detailed explanation of how they will recruit the target population and address the issues of consent for participants and demonstrate the support of appropriate clinicians and centres with sufficient capacity to undertake the pilot study or the full trial.

1. **Technology:** Low-Dose Spiral Computerised Tomography (CT) scanning.
2. **Patient group:** Researchers should identify and justify the selection of a suitable target population in the UK.
3. **Setting:** A UK population based screening programme.
4. **Design:** The design is to be a controlled trial. The protocol for the trial should be powered at the level of 90% or greater.
5. **Comparator:** Unscreened population receiving standard care
6. **Primary outcome** Lung cancer mortality rate.
7. **Secondary Outcomes** (informed by NSC criteria): The diagnostic accuracy of spiral CT in a screening population (sensitivity and specificity), lung cancer detection rates, harms within a UK secondary care setting, psychological impact, quality of life, screening uptake and acceptability, pre & post screening smoking status and estimates of the cost-effectiveness and cost utility of screening.
8. **Intermediate results:** A report is required at the end of the pilot study to help the HTA programme come to a timely decision about the viability of proceeding to the full trial. This

should include any proposals for varying parameters or other aspects of the trial and if appropriate, revisions to the proposed costs.

9. **Duration of follow up**. The duration of the pilot study and the full trial should be justified in the proposal.

Background to commissioning brief:

In 2006, the NHS HTA Programme working with the UK National Screening Committee (NSC), commissioned a review of the evidence base for the clinical effectiveness of using spiral CT for lung cancer screening [HTA 2006 Vol 10(3)]. The main conclusions of the report were that the evidence base was still insufficient to demonstrate a reduction in mortality from a programme of CT screening.

The report identified a number of important research priorities including the development of a RCT to identify the effect of CT on mortality; obtain UK data about the rate of positive screening with CT and detected lung cancers; the natural history and epidemiology of screening; and the impact of screening on quality of life and acceptability and uptake.

The UK National Screening Committee (NSC) has set out clear "Criteria for appraising the viability, effectiveness and appropriateness of a screening programme" that should be met before a decision could be made about the potential for introduction of any new screening programme in the UK. It is the intention of this study that as many of the uncertainties that remain affecting the potential effectiveness of any future screening programme should be resolved within the proposed study.

The NSC criteria most relevant to this proposal are: 2, 5-7, 10, 13, 14 and 15. Criteria 3, 12, 16 and 19 lie outside the remit of this study.

Further information to be considered in the feasibility study

This commissioning brief sets out the requirements for the feasibility study. Proposals for the feasibility study should include descriptions of the techniques and modelling that will inform the ultimate choice of parameters to be adopted within the protocol, initially within the pilot study and subsequently in the main trial. The opportunity should be taken during the pilot study to refine a number of the parameters to be used within the main trial, should it proceed.

The feasibility study should model and present information showing the effect of variations in a range of parameters within the screening programme including: diagnostic accuracy, altering the criteria used to define the target group, the age of initial screen, the potential screening interval (if any), the impact of variations in uptake of screening and other aspects relevant to the NSC criteria.

To justify the design and parameters selected within the trial, outcomes will need to be modelled for these different scenarios and should include mortality, the harmful consequences of screening from point of invitation through investigation \and treatment and include an assessment of cost effectiveness and quality of life.

The feasibility study should review the design of the European (NELSON) trial and in the light of their analyses consider and explain whether joining the NELSON trial might provide a cost effective option to answer the issues required by this commissioning brief. If not, it must identify to what extent existing studies, including NELSON and the National Lung Screening Trial (USA) could be used to add value to the proposed trial protocol and if relevant, how they would be incorporated into analysis e.g. to enable combined analysis of study data with estimates of the potential effect on the required sample size, study duration and cost of the proposed UK trial.

Proposals will need to demonstrate the practical feasibility of the proposal in terms of a broad level of clinical support across relevant specialties in appropriate centres willing to participate in either the pilot study or a full trial and the availability of appropriate capacity and infrastructure to support this commitment.

The pilot study and proposed trial will need to collect detailed data on resource use sufficient to inform the development of an economic model both for assessment of the cost effectiveness and cost utility of the intervention and also to allow estimation of the potential cost and infrastructure needed for implementation of a 'national' screening programme.

The HTA commissioning process

The process that will be adopted by the HTA Programme in this case is similar to that for all HTA funded research. It is important when putting forward a proposal that the researchers contributing to the feasibility study comprises a strong team with sufficient experience and skills to address the breadth of clinical, radiological, psychological and methodological (statistics/ modelling/ health economics) issues required as well as individuals with a track record of undertaking major multi centre clinical trials.

There are 3 key phases to this process:

1. Proposals for undertaking a feasibility study must be received by 13.00 hrs on 12th March 2008. They will be peer reviewed and then considered by an HTA Board and assessed on their practicality, scientific quality and value for money. If there are sufficient applications more than one feasibility study may be funded.

   It is envisaged that the work of developing a detailed protocol with supporting commentary and analysis may take six or seven months and will be completed and submitted no later than 13.00 hrs on 31st March 2009.

   There will then be a period during which the completed feasibility studies and trial protocols will be peer reviewed at the end of which an 'HTA Commissioning Board' will consider the protocols and supporting evidence and consider the practicality, scientific quality and value for money of proposals for the pilot study and clinical trial.

2. If judged of sufficient quality and feasibility the 'best' proposal for a pilot study and clinical trial will be commissioned (subject to any necessary changes) from the same team as part of a 2 stage process. Initial funding will be provided to undertake the pilot study following which the report and outcome of the pilot will be reviewed and assessed by an HTA Board.

3. If satisfactory, the same research team will be invited to propose modifications to the full trial and to submit an amended trial protocol. Subject to satisfactory modification to the trial protocol, feasibility and value for money a full NIHR HTA Screening trial will be commissioned subject to funding availability.

Notes to Applicants

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. 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 a proposal on this topic, complete the electronic application form and return it, along with a detailed project description, to the HTA Commissioning Manager at the National Coordinating Centre for Health Technology Assessment, Mailpoint 728, Boldrewood, University of Southampton, Southampton SO16 7PX by **12 March 2008**.

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

Please see GUIDANCE ON APPLICATIONS overleaf.

Guidance on applications

Methods

Applicants should demonstrate knowledge of current research in the field and of systematic review methods and state how these would apply to the question posed. Valid and reliable methods should be proposed for identifying and selecting relevant material, assessing its quality and synthesising the results. Guidance on choice of appropriate methods is contained in NHS CRD Report 4 *Undertaking systematic reviews of research on effectiveness* (www.york.ac.uk/inst/crd/report4.htm). Where policy implications are considered, the emphasis should be on assessing the likely effects of a range of policy options open to decision makers rather than a judgement on any single strategy. Where epidemiological modelling or economic evaluation is required, the range of uncertainty associated with the results should be assessed. In the assessment of cost-effectiveness, further data collection may be required to estimate resource use and costs. If there is evidence that the ratio of costs and benefits may differ between readily identifiable groups, applicants are encouraged to state how they will identify these differences.

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 research may be to assess the effects of such changes on patient outcome.

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.

Updating

It is the policy of the NCCHTA that all search strategies undertaken as part of evidence synthesis/secondary research projects must not be more than 12 months out of date when the draft final report is submitted. We expect that most projects will manage to bring their searches up to date prior to analysis and writing up. As research funders we are aware that exceptional circumstances can apply that would not allow this to be case but this must be the exception rather than the rule and will be assessed on a case by case basis. The expectation is that projects funded by the HTA programme will deliver information that is both relevant and timely.

In addition, in order to inform decisions on whether and when to update the review, researchers will be expected to give some indication of how fast the evidence base is changing in the field concerned, based on the nature and volume of ongoing work known at the time the review is completed. Applicants should note that they will not be expected to carry out any future updating as part of the contract to complete the review.

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 to the HTA programme. They are also required to communicate their work through peer-reviewed journals 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

The deadline for completion of this project is fixed and it is for applicants to justify the costs proposed.