Health Technology Assessment Programme

NHS National Institute for Health Research

HTA no 17/86

The clinical and cost effectiveness of screening for Group B Streptococcus (GBS) in pregnancy

Introduction

The aim of the HTA Programme is to ensure that high quality research information on the effectiveness, costs and broader impact of health technology 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.

Research Question:

Does screening women for carriage of GBS in late pregnancy or labour reduce the occurrence of early onset neonatal sepsis? Do the benefits outweigh the harms and would screening be cost effective?

1. **Intervention:** A defined pathway for screening and treatment of women, using the 'best' available test for GBS. Applicants should justify the choice and timing of the test in the context of the evidence base and consider the potential of new rapid testing technologies. Proposals should explain how women in the 'higher risk' groups are to be managed in the pathway.
2. **Patient group:** Pregnant women.
3. **Setting:** Appropriate acute and community settings.
4. **Comparator:** Women managed according to current best practice (*RCOG Guidance*).
5. **Study design:** A cluster randomised control trial building on an internal pilot trial with clear continuation criteria and informed by a concurrent feasibility study. A model of cost effectiveness is required. Quality assurance processes for the screening pathway should be described and evidence based information developed for patients and midwives. The definition of sepsis, including for culture negative results must be defined.
   a) An internal pilot trial of sufficient duration to explore aspects of deliverability e.g. enrolment of sites, acceptability and uptake of screening and intrapartum antibiotic prophylaxis (IAP), fidelity in both trial arms.
   b) Qualitative work during the pilot trial should identify facilitators and barriers to effective implementation of the trial, with rapid analysis to inform delivery of the intervention.
   c) The feasibility study should explore how changes in achievement of key study parameters in both arms of the trial will affect the robustness of the overall findings.

   The successful applicants are encouraged to work with additional collaborators to enhance the understanding of issues such as; the epidemiology of GBS colonisation, transmission or pathogenicity and any effects of IAP on antimicrobial resistance, etc.
6. **Important outcomes for the main trial:** Applicants to specify and justify their choice of primary outcome of a reduction in either (1) severe early onset neonatal GBS sepsis; or (2) severe all cause early onset neonatal sepsis.

   Other outcomes: Neonatal mortality (all cause and from sepsis); serious neonatal morbidity (applicants to define); adverse events for mother or baby; resources used for implementation; cost effectiveness.

For the pilot trial: Site enrolment and participation; acceptability and uptake of screening and IAP treatment; fidelity to the intervention and the control arm; adverse outcomes for woman or neonate; onset of neonatal sepsis. Findings of the feasibility study.

Minimum duration of follow-up: For the main trial 4 weeks post-delivery. Applicants should consider the use of routine data sources for outcome determination and how consent for collection of longer-term outcomes might be achieved.

NHS decision problem to be addressed by this research:

Group B Streptococcus (GBS) is a common form of bacteria, present in both men and women and is usually harmless. However, the bacteria can pass from the mother to her baby in labour and a very small proportion of babies will develop early onset GBS infection. It is not possible to predict which babies will be affected, although with treatment most babies recover fully. In a small number of cases the infection can result in serious illness, long term disability or death.

Giving intravenous antibiotics to the mother during labour has been shown to reduce the risk of her baby developing GBS infection. However, there are concerns that large numbers of women will be given antibiotics when they do not need them and that the longer-term effects of antibiotics on mother and baby are unknown. There may also be adverse effects on antimicrobial resistance.

Although GBS screening is undertaken in some countries the evidence for its clinical and cost effectiveness is still uncertain. In the U.K., current guidance is based on a strategy of identifying and treating women who are in 'high risk' categories.

The U.K. National Screening Committee has reviewed the evidence for screening for GBS on a number of occasions, most recently in March 2017 and has concluded that a "Systematic population screening programme is not recommended".

In January 2017, the English Department of Health convened a workshop to consider the issues of GBS disease and concluded that a randomised trial of screening was needed to try and resolve the uncertainties around the likely effectiveness GBS screening.

The NIHR HTA programme is aware that during the development of this trial new data may become available on the use of more sensitive and rapid tests. These tests could provide an opportunity to consider screening strategies that may be more efficient than those based on swab testing and culture.

Applicants invited to submit a full proposal should include evidence of the commitment of sufficient hospitals, midwifery services and commissioners to deliver a trial of the size required to provide a robust answer to this research call.

If potential applicants wish to discuss this call with representatives of the National Screening Committee and Public Health England contact details can be obtained from the HTA secretariat (htacommissioning@nihr.ac.uk).

Notes to Applicants

The NIHR Health Technology Assessment Programme is funded by the NIHR, with contributions from the CSO in Scotland, Health and Care Research Wales, and the Public Health Agency in Northern Ireland.

For many of the research questions posed by the HTA Programme, a randomised controlled trial is the most appropriate method of providing an answer. Suggestions for how a randomised controlled trial could be designed and constructed most efficiently are encouraged. Where the study design has been

left open for applicants to specify, please note that the HTA Programme welcomes any study design which is well justified as the most appropriate approach to answer the research question.

Applicants are asked to:

1. Follow the Medical Research Council's (MRC) Good Clinical Practice guidelines (http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/) 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 NIHR website (http://www.ct-toolkit.ac.uk/) also contains the latest information about Clinical Trials regulations and a helpful FAQ page.

In line with the government's transparency agenda, any contract resulting from this tender may be published in its entirety to the general public. Further information on the transparency agenda is at: http://transparency.number10.gov.uk/#

Applicants are recommended to seek advice from suitable methodological support services, at an appropriate stage in the development of their research idea and application. It is advisable to make contact at an early a stage as possible to allow sufficient time for discussion and a considered response.

The NIHR Research Design Service (http://www.rds.nihr.ac.uk/) can advise on appropriate NIHR Programme choice, and developing and designing high quality research grant applications.

Clinical Trials Toolkit

Researchers designing or undertaking clinical trials are encouraged to consult the Clinical Trials Toolkit (www.ct-toolkit.ac.uk). This NIHR resource is a website designed to help researchers navigate through the complex landscape of setting up and managing clinical trials in line with regulatory requirements. Although primarily aimed at those involved in publicly funded Clinical Trials of Investigational Medicinal Products (CTIMPs), the Toolkit will also benefit researchers and R&D staff working on trials in other areas, who will find useful information and guidance of relevance to the wider trials environment.

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 stage one application against this topic, complete the on-line application form at www.nihr.ac.uk/funding-and-support/current-funding-opportunities/ the HTA Programme can be selected using the filters and submit it on line by **30 November**. Applications will be considered by the HTA Funding Board at its meeting in **January 2018**.

IMPORTANT: For stage one applications, if shortlisted, investigators will be given a minimum of **eight weeks to submit a full proposal**. The full proposal will be considered at the Funding Board in **May 2018.**

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

Please see GUIDANCE ON APPLICATIONS overleaf.

Should you have any queries please contact: htacommissioning@nihr.ac.uk
Telephone: Commissioning Board 02380 595510

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, behavioural science 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 benefit of 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 *could* be improved by involving members of the public. Examples of how this has been done for health technology assessment projects can be found at www.nets.nihr.ac.uk/ppi. 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. Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established. 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. Where relevant, researchers should explore the effect of the intervention in relation to health inequalities. These factors should guide applicants in their choice of subjects, settings and measurements made.

Longer-term follow up

Researchers to consider building in provision, if appropriate, for a simple mechanism for long-term follow up using routine data bases/sets; including obtaining consent for this from participants at trial entry.

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 NETSCC, HTA 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.

Feasibility and Pilot studies

We expect that when pilot or feasibility studies are proposed by applicants, or specified in commissioning briefs, a clear route to the substantive study will be described. This applies whether the brief or proposal describes just the preliminary study or both together. Whether preliminary and main studies are funded together or separately may be decided on practical grounds.

Feasibility Studies are pieces of research done before a main study. They are used to estimate important parameters that are needed to design the main study. Feasibility studies for randomised controlled trials may not themselves be randomised. Crucially, feasibility studies do not evaluate the outcome of interest; that is left to the main study. If a feasibility study is a small randomised controlled trial, it need not have a primary outcome and the usual sort of power calculation is not normally undertaken. Instead the sample size should be adequate to estimate the critical parameters (e.g. recruitment rate) to the necessary degree of precision.

Pilot studies are a version of the main study that is run in miniature to test whether the components of the main study can all work together. It is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It will therefore resemble the main study in many respects. In some cases this will be the first phase of the substantive study and data from the pilot phase may contribute to the final analysis; this can be referred to as an internal pilot. Or at the end of the pilot study the data may be analysed and set aside, a so-called external pilot.

For a full definition of the terms 'feasibility study' and 'pilot study' visit the NETSCC website glossary page www.nets.nihr.ac.uk/glossary

In preparing for a substantive evaluation attention should be paid to appropriate guidance on how to develop interventions (such as the MRC guidance on developing and evaluating complex interventions and the IDEAL framework: www.ideal-collaboration.net/framework/).

Diagnostics and Imaging

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.