Health Technology Assessment Programme

NHS National Institute for Health Research

Australian Government

National Health and Medical Research Council

HTA no 13/154

Early warning signs of relapse in schizophrenia

This topic has been identified as an opportunity for collaboration between Australia's National Health and Medical Research Council (NHMRC) and the UK National Institute for Health Research (NIHR) HTA programme and we welcome joint applications from Australian and UK researchers.

Introduction

HTA Programme
The aim of the Health Technology Assessment (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.

National Health and Medical Research Council
The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research; for developing health advice for the Australian community, health professionals and governments; and for providing advice on ethical behaviour in health care and in the conduct of health and medical research. The NHMRC mission statement is 'Working to build a healthy Australia'. Further information is available at the NHMRC website: http://www.nhmrc.gov.au/.

Research Question:

How feasible is a study to investigate the clinical and cost-effectiveness of an intervention to recognise and promptly manage the early warning signs of recurrence in schizophrenia with the aim of preventing relapse?

1. **Intervention:** An intervention as an adjunct to usual care that is easily deliverable in the NHS (or the equivalent Australian community setting) and (i) enhances the recognition of early warning signs by patients and their carers and (ii) provides a pathway, that is either self-activated or in liaison with a community healthcare professional, which then triggers a relapse prevention strategy to reduce the likelihood of a psychotic relapse. The elements of intervention should be defined and justified by applicants, including who would deliver them.
2. **Patient group:** Adults with schizophrenia and their carers - exact inclusion criteria to be defined by applicants. Consideration should be given to patients without carers, to coexisting substance abuse and to issues of medication compliance.
3. **Setting:** Community.
4. **Control:** Treatment as usual reflecting current UK/Australian practice – to be defined by applicants.
5. **Study design:** Feasibility study to develop and manualise an appropriate intervention and to define treatment as usual as clearly distinct from the intervention. The intervention should be evaluated by means of an external pilot randomised controlled trial to test recruitment,

acceptability and outcome measures. Applicants are encouraged to use the updated MRC framework for complex interventions. *A decision on whether to advertise for a substantive trial will be made in light of the results of this feasibility study.*

6. **Important outcomes:** Manualised intervention; estimate of acceptability to patients and carers; feasibility of proceeding to a full trial; appropriate outcome measures that could be used in a longer term main study such as: relapse rate, time to relapse, hospitalisation, negative and positive symptomatology, adverse events, emotional adjustment, carer burden and health related quality of life.

Decision problem to be addressed by this research:

Schizophrenia is the commonest form of psychosis. Most often it has a cyclical pattern characterised by acute psychotic episodes followed by full or partial remission of psychotic symptoms. Early warning signs (EWS) that are idiosyncratic to the person with schizophrenia (such as a deterioration of personal hygiene, unexpected hostility, increasing paranoia etc.) often precede an acute psychotic relapse. If patients and carers are trained to recognise and then promptly manage these EWS via a relapse prevention strategy (for example by adopting short-term additional treatments such as diazepam, additional oral antipsychotic or cognitive therapy), psychotic relapse might be prevented, delayed or its impact minimised. Although there are obvious potential health benefits for patients, as well as cost savings for the health service, adverse outcomes should also be considered.

A recent Cochrane review found only low quality evidence to suggest a positive effect of EWS interventions on the proportion of people re-hospitalised and on rate of relapse. The majority of included studies involved training in EWS alongside other psychological therapies. Although EWS interventions are carried out in routine clinical care for people with schizophrenia, their availability and delivery vary considerably from one clinical service to another even in the same locality. The proposed feasibility study could pave the way for a trial that could help inform and formalise clinical practice.

Process for UK only applications
Please refer to Sections A and C for guidance notes

Process for joint UK and Australian applications
In Section A below please see the guidance notes for the UK based research and in Section B below please see guidance notes for the Australian based research. These should be read in conjunction with each other. Please also see Section C and note the following points:

- In the first instance, a joint outline application must be made via the NIHR HTA programme using the online application form.
- Shortlisted applicants will subsequently be invited to submit a full application to the NIHR HTA programme.
- Concurrently, the Australian team will also be required to submit the full NHMRC application to NHMRC via its Research Grants Management System (RGMS) for the purpose of review of the requested budget for the Australian part of the collaboration.
- The UK based research will be funded by the NIHR HTA programme and the Australian based research by the NHMRC. Australian based researchers must be affiliated with an NHMRC approved Australian Administering Institution.
- The NIHR online application form will require one chief investigator who can be based in the UK or in Australia.
- The NIHR HTA programme must contract with a UK institution and requires a UK sponsor.
- For Australian collaborations, an Australian clinical trials sponsor is also required.
- For a glossary of terms for investigators please see the end of the document.

Making an application

If you wish to submit an outline proposal on this topic, complete the on-line application form at www.nets.nihr.ac.uk/funding/hta-commissioned and submit it on-line by **8th May 2014**. Applications will be considered by the HTA Commissioning Board at its meeting in **July 2014**. For outline applications, if shortlisted, investigators will be given a minimum of eight weeks to submit a full proposal.

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

Section A: Guidance notes for the UK based research (to be read in conjunction with Section B for joint UK and Australian applications)

The NIHR Health Technology Assessment Programme is funded by the NIHR, with contributions from the CSO in Scotland, NISCHR in Wales, and the Public Health Agency in Northern Ireland.
NHMRC will provide funding for Australian researchers collaborating with UK researchers.

Australian applicants should refer to Section B for eligibility criteria.

For many of the questions posed by the HTA Programme 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.

UK applicants are asked to:

1. Follow the Medical Research Council's Good Clinical Practice guidelines (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416) 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 UK-based trials involving medicinal products must comply with "The Medicines for Human Use (Clinical Trials) Regulations 2004". In the case of such trials, the UK Department of Health (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 in the UK (info@mhra.gsi.gov.uk, http://www.mhra.gov.uk) can provide guidance as to whether your trial would be covered by these regulations. The DH/MRC website (http://www.ct-toolkit.ac.uk/) contains the latest information about Clinical Trials regulations and a helpful FAQ page.

In line with the UK 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.

In the UK the NIHR Research Design Service (www.nihr.ac.uk/research/Pages/ResearchDesignService.aspx) 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 in the UK.

Australian applicants should refer to Section B for equivalent information to the above, relevant to conducting clinical trials in Australia.

Section B: Guidance notes for the Australian based research (to be read in conjunction with Section A)

For this topic, NHMRC has allocated a total of up to AUD 1.5 million to support the Australian-based component of a collaboratively funded project within the NIHR Health Technology Assessment Programme. The information in this section is to assist researchers proposing joint applications with UK investigators. NHMRC grants offered will be of up to five years duration to support the Australian-based components of collaborative research grants.

Australian Partner Investigators

Details of the Australian components of the project are to be included in the outline proposal and, where invited, the subsequent full application submitted to the NIHR HTA Programme. Submission of the NIHR joint outline proposal and full application are the responsibility of the chief investigator.

Australian Partner Investigators on a joint application that is awarded funding by the NIHR HTA programme will subsequently need to submit a formal application in NHMRC's Research Grant Management System for the purpose of reviewing the requested Australian budget. The application submitted to NHMRC should provide justification for the requested budget including Personal Support Packages (PSP), Direct Research Costs (DRCs) and Equipment. This budget will be reviewed by NHMRC and may by adjusted as appropriate.

Applicants should ensure that the budget submitted to the NIHR HTA programme for the Australian component of the project is compatible with standard NHMRC budget requirements.

The Partner Investigator named in the application to the NIHR HTA programme will be required to be the Chief Investigator A (CIA) on the NHRMC application. The CIA takes the lead role in the conduct of the Australian component of the research project, and is responsible for completion and lodgement of the NHMRC application. Partner Investigators will be given the opportunity to list key members of the research team based in Australia as Chief Investigators B-J.

It is an eligibility requirement for NHMRC funding that the CIA on the NHMRC application be an Australian citizen or permanent resident at the time of submission, and must be based in Australia for the duration of the grant. Applications must be submitted through an NHMRC-approved Administering Institution.

Provision of NHMRC support will generally be in accordance with established NHMRC policies and procedures.

NHMRC funds the direct costs of the research proposal. Applicants should refer to *NHMRC Direct Research Costs* ***Guidelines*** available at:
http://www.nhmrc.gov.au/_files_nhmrc/file/grants/funding/funded/manage/policy/drc_principles%20guidelines_1%20january_2014.pdf

Enquiries regarding NHMRC funding support should come from the Research Administration Office (RAO) of the CIA's Administering Institution in the first instance. If further assistance is required, please contact the NHMRC Research Help Centre in Australia on 1800 500 983 or help@nhmrc.gov.au

Please Note:

The NIHR HTA programme will have additional requirements of successful applicants beyond those the NHMRC normally request. These include, but are not limited to:

1. Six monthly progress reporting to the NIHR HTA programme including data for patient recruitment to trials. If an issue is identified with the recruitment then the frequency of reporting would be increased. NIHR also require a mechanism to halt/terminate trials that are not on track.
2. Publication of research findings (peer reviewed final reports) in the NIHR HTA journal.

Requirements for conducting clinical trials in Australia

All proposals to conduct a clinical trial in Australia require ethical review and approval by a human research ethics committee (HREC). A HREC must have notified its existence to the Australian Health Ethics Committee (AHEC) of the NHMRC and provided assurances that it is operating within NHMRC guidelines.

Therapeutic Goods Administration - Trial compliance

Australia-based clinical trials involving the administration of drugs, chemical agents or vaccines to humans may require approval by the TGA, which administers the Clinical Trials Notification (CTN) /Exemption (CTX) Schemes. This does not apply to clinical trials in which registered or listed medicines or medical devices are used within the conditions of their marketing approval.

For further information on the regulation of clinical trials in Australia, please visit the TGA website at http://www.tga.gov.au/industry/clinical-trials.htm

The Australia Clinical Trials Handbook (TGA Health and Safety Regulation)

It is recommended that applicants for funding to support clinical trials research in Australia consult the following resources for additional information:

- the Australian clinical trial handbook (http://www.tga.gov.au/industry/clinical-trials-handbook.htm); and
- the Australian Clinical Trials website: http://www.australianclinicaltrials.gov.au/researchers

Good Clinical Practice guidelines

The GCP Guidelines represent an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human participants. The Therapeutic Goods Administration (TGA) has adopted the European Union version of GCP guidelines in Australia. The guideline should be followed when submitting clinical trial data to the TGA.

http://www.australianclinicaltrials.gov.au/node/36

Trial Sponsor(s)

Applicants who are asked to submit a full proposal will need to obtain confirmation of a sponsor(s) to complete their application. All trials must have an Australian sponsor. *Please note that a UK sponsor will also be required by the NIHR HTA programme.* The sponsor is that person, body, organisation or institution which takes overall responsibility for the conduct of the trial. The sponsor usually initiates, organises and supports a clinical study and carries the medico-legal responsibility associated with the conduct of the trial.

Trial registration

All NHMRC funded clinical trials must also be registered in the Australia and New Zealand Clinical Trials Registry (ANZCTR), or equivalent, prior to commencement of the clinical phase. Information pertaining to the ANZCTR or equivalent, and how to register can be found at: http://www.anzctr.org.au.

Section C: 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 and NHMRC recognise the benefit of increasing active involvement of members of the public in research and would like to support research projects appropriately. The HTA Programme and NHMRC encourage 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. NHMRC also has a statement on consumer and community participation in health and medical research, available from the NHMRC website http://www.nhmrc.gov.au/guidelines/publications/r22-r23-r33-r34 . 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. 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 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. **The Australian-based researchers of collaborative projects are also required to submit a final report to NHMRC.**

Timescale

The NIHR HTA programme has 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. *Australian applicants should note that NHMRC has a maximum funding duration of five years so this will need to be taken account of in the application.*

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

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.

Glossary of terms used for investigators

UK terms:

Chief Investigator: The person applying for the money and who holds the contract and is ultimately responsible for delivering the project.

Australian terms:

Partner Investigators: Members of the Australian research team collaborating with the lead UK research team
Chief Investigator A (CIA): Leader of the research group in Australia. The Australian part of the project is usually administered by the host institution of the CIA. The CIA is responsible for ensuring that the Australian team meets its reporting and other obligations.
Chief Investigator B-J: Additional members of the Australian research team.
Administering Institution: The NHMRC approved institution in Australia that applies to NHMRC for funding and that administers grants awarded by the NHMRC. The Administering Institution is usually the host institution of the CIA.