Topiramate for posttraumatic stress disorder

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 in addition to standalone applications from UK based researchers.

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.

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/](http://www.nhmrc.gov.au/).

Research Question:

What is the clinical and cost-effectiveness of topiramate for patients with posttraumatic stress disorder (PTSD) who have not responded to first line treatments?

1. **Intervention:** Topiramate (applicants to define and justify the dose regimen) plus ongoing treatment.
2. **Patient group:** Adults with PTSD that have responded inadequately to trauma-focused psychological therapy and a course of antidepressant medication – exact inclusion criteria to be defined and justified by applicants. The PTSD should have arisen as a result of adulthood life events. Special consideration should be given to the co-occurrence of alcohol/substance use disorder. In addition, consideration should be given to any other treatments the patients may be receiving as part of their care, and to any other co-morbid conditions.
3. **Setting:** Specialist mental health services – to be defined by applicants.
4. **Control:** Placebo plus ongoing treatment.
5. **Study design:** A two arm randomised controlled trial (RCT). There should be an internal pilot phase to test recruitment with clear stop/go progression criteria to the full trial.
6. **Important outcomes:** PTSD symptom severity, remission, and discontinuation rates; adverse events.
   - **Other outcomes:** Health related quality of life; substance abuse; mood; cost-effectiveness; patient acceptability; need to switch to an alternative treatment.
7. **Minimum duration of follow-up:** One year.
Notes to Applicants

Process for UK only applications

Please refer to Sections A and C for the guidance notes.

Process for joint UK and Australian applications

Please refer to Section A for guidance notes for the UK based research and Section B for the 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 Expression of Interest (EoI) 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. The budget for the Australian component of research should be submitted to NIHR HTA as an additional upload to accompany submission of the full application, these costings should be in line with NHMRC requirements.
- The Australian team on shortlisted applications will be required to submit an 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 full application submitted to NIHR is required to be uploaded to RGMS (as a PDF) as part of the Australian application.
- 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 will be based in the UK or in Australia.
- For Australian collaborations, an Australian clinical trials sponsor is also required. Refer Part B for further information.
- For a glossary of terms for investigators please see the end of the document.

NHS decision problem to be addressed by this research:

PTSD arising from adulthood traumatic events is a common psychiatric condition in veteran and civilian populations. NICE guidelines recommend trauma-focused psychological therapy as first line treatment whereas the recent British Association for Psychopharmacology (BAP) guideline recommends either trauma-focused psychological therapy or evidence-based medication (paroxetine, sertraline, venlafaxine). It has been reported that many people with severe PTSD do not have a satisfactory response to these treatments. This has led to repeated suggestions that further investigation into other pharmacologic agents for the treatment of PTSD is warranted for those patients who have failed to respond to first line treatments.

Topiramate is an anticonvulsant licensed in the UK to treat seizures in children and adults, as well as adult migraines. It has demonstrated promising results as an off label medication in RCTs with civilians and veterans with PTSD, including those with comorbid alcohol abuse. Despite possible side effects, studies so far have reported that these were not considered to be serious. Compared to the drugs recommended for PTSD by the BAP guideline, a recent meta-analysis found that topiramate was more effective than sertraline and venlafaxine but was not significantly different from paroxetine. However, the results for topiramate came from only three small trials so further studies were suggested. A RCT is needed that gives careful consideration to the balance of benefits and risks of prescribing topiramate for PTSD.
Making an application

If you wish to submit an Expression of Interest 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 23 November 2017. Applications will be considered by the HTA Funding Board at its meeting in January 2018.

IMPORTANT: For Expressions of Interest, 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.

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, Health and Care Research 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 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 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 stage as possible to allow sufficient time for discussion and a considered response.

The NIHR Research Design Service (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.

*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)¹

NHMRC has allocated a total of up to AUD 3 million to support Australian-based components of collaboratively funded projects 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.

NIHR reserve the right to fund and proceed with only the UK component of joint UK/ Australian collaborative studies, on a case-by-case, should fundable projects exceed the allocated NHMRC budget. NIHR will not fund the international component of collaborative studies.

**Australian based research**

**Australian Partner Investigators**

The Australian Partner Investigator named in the application to the NIHR HTA programme will be required to be the Chief Investigator A (CIA) on the NHMRC 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. The CIA will be given the opportunity to list key members of the research team based in Australia as Chief Investigators B-J.

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¹ Australian applicants should also ensure they read and understand application requirements as outlined in the NHMRC Funding Rules 2017 and the Scheme-Specific NHMRC-NIHR Collaborative Grants Funding Rules 2017
At time of acceptance and for the duration of the grant, the CIA must be an Australian citizen or permanent resident of Australia or have an appropriate work visa in place. The CIA must also be based in Australia for at least 80 percent (%) of the funding period.

Applications must be submitted through an NHMRC-approved Administering Institution.

NHMRC Funding is provided by the Australian Government and administered in accordance with the NHMRC Funding Agreement. Funding is provided to the Administering Institution, which is responsible for the grant administration.

**Australian based research proposal and budget**

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

Australian Partner Investigators on a joint application that is shortlisted by the NIHR HTA programme will also need to submit a formal application in NHMRC’s RGMS for the purpose of reviewing the requested budget for the Australian part of the collaboration. 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 be 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 as outlined at:


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.


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.

Please see GUIDANCE ON APPLICATIONS overleaf.

Should you have any queries please contact htccommissioning@nihr.ac.uk
Or telephone 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.nihr.ac.uk/patients-and-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. 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.

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.
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.

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.nihr.ac.uk/glossary](http://www.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/](http://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.