Health Technology Assessment

Higher-calorie refeeding compared with lower-calorie refeeding in malnourished adults with anorexia nervosa

Overview

Opportunity status:	Open
Type:	Programme
Opening date:	28 November 2024 at 1:00 pm
Closing date:	2 April 2025 at 1:00 pm
Reference ID:	2024/203

Ready to apply?

Apply for this funding opportunity through our online application form

Apply now

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Our Health Technology Assessment (HTA) Programme (/research-funding/funding-programmes/health-technology-assessment) is looking to fund research into higher-calorie refeeding compared with lower-calorie refeeding in malnourished adults with anorexia nervosa.

This is a two-stage, commissioned funding opportunity. To apply for the first stage you should submit an Outline Application. If invited to the second stage, you will then need to complete a Full Application.

Eligibility

See our HTA Programme page for eligibility on what we will fund.

Key dates

28 November 2024

Outline Application opening date

2 April 2025

Outline closing date

Mid-May 2025

Outline Application funding committee meeting

Late May

Outline Application decisions notified

Late May

Full Application opening date

17 July 2025

Full Application closing date

Mid-September 2025

Full Application funding committee meeting

Mid-October 2025

Full Application decisions notified

Studies within a trial or review

This funding opportunity is eligible for a SWAT/SWAR (study within a trial or study within a review), which can help significantly improve methodology of future research as well as the host study. Find out about the benefits of SWATs/SWARs and how to include one in your application (https://www.nihr.ac.uk/methodological-sub-studies-studies-within-trial-or-project-swat-and-studies-within-review-swar).

Webinar

We will be holding a webinar to support this funding opportunity on Monday 20 January 2025 at 10am. This session will provide an opportunity for attendees to ask any questions.

If you would like to attend, please contact htaresearchers@nihr.ac.uk (mailto:htaresearchers@nihr.ac.uk) for joining information.

Funding applications must be submitted via our Awards Management System. Click the link below to log in to the system and start your application.

Apply now

ps/app_viewopportunity.jsp%3Fappid%3D105112%26nextlevel%3D1%26opportunityid%3D10082504)

Research specification

The aim of the HTA Programme is to ensure that high quality research information on the clinical effectiveness, cost-effectiveness and broader impact of healthcare treatments and tests are produced in the most efficient way for those who plan, provide or receive care from NHS and social care services. The commissioned workstream invites applications in response to calls for research on specific questions which have been identified and prioritised for their importance to the NHS, patients and social care.

Research questions

(a) Is it feasible to conduct a study to examine the effectiveness of higher-calorie refeeding compared with lower-calorie refeeding in malnourished adults with anorexia nervosa?

(b) If feasibility is established, what is the clinical and cost-effectiveness of higher-calorie refeeding compared with lower-calorie refeeding in malnourished adults with anorexia nervosa?

1. Patient group

Adults with a diagnosis of anorexia nervosa who are (a) malnourished and require inpatient refeeding and (b) have at least one risk factor for refeeding syndrome. Applicants to define and justify exact criteria.

2. Intervention

Higher-calorie refeeding, for example, 30-35kcal/kg per day. Applicants to define and justify exact amount and method of refeeding.

3. Comparator

Lower-calorie refeeding, for example, 10-20kcal/kg per day. Applicants to define and justify exact amount and method of refeeding.

4. Setting

Secondary care. Applicants should include a range of secondary care settings e.g., medical units, specialist eating disorder units and clinical nutrition units.

5. Study design

A two stage design starting with a feasibility study leading into the full trial (if indicated). Applicants should describe in detail how the feasibility study will be assessed to inform progression between the feasibility study and the full trial.

Applicants are encouraged to:

- collaborate with a Clinical Trials Unit (CTU)
- ensure that the research team is multi-disciplinary, e.g., eating disorder specialists, gastroe nterologists, etc.
- include wide engagement during the feasibility stage (i.e. beyond the feasibility sites) to ensure that recruitment would work well in a full trial.

Stage one: A feasibility study to determine whether future effectiveness research is possible and to establish key parameters of a potential future study. This includes:

- the ability to recruit and randomise in different secondary care settings
- an understanding of equipoise in the patient community and among clinicians
- the acceptability of the intervention to patients and clinicians
- describing sample size parameters
- the proposed calorie intake for the intervention and comparator arms
- the important outcome

Applicants should indicate the likely duration of the feasibility study.

Please note:

- The decision will be made by the HTA Programme whether to move from the feasibility study (stage one) to the full trial (stage two) based on the agreed outcomes of the feasibility study.
- Applicants will not be required to complete full follow up for the clinical outcomes before a decision is made whether to progress to a full trial. This is to ensure that if important feasibility outcomes, such as the ability to open centres, recruit and randomise are met, that there is no unnecessary delay in moving to a full trial.

Stage two: A randomised controlled trial to evaluate the clinical and cost effectiveness of higher-calorie refeeding compared with lower-calorie refeeding. Applicants should consider whether individual randomisation, cluster randomisation or a step-wedge design should be used and justify their decision. (The study design for Stage two will be reviewed in the light of the outcomes of Stage one.)

6. Outcomes

Refeeding hypophosphatemia; instances of refeeding syndrome; time to establishment of target feeding rate(in days); cardiovascular measures; assessment of biochemical and haematological responses to refeeding; weight measures e.g., weight change, BMI, percentage mBMI; length of hospital stay; readmission, number of readmissions; quality of life; mental health; adverse events; death; cost effectiveness.

7. Minimum duration of follow-up

Minimum follow-up of one year from randomisation but applicants should define and justify the most appropriate timing of the primary outcome measure.

Longer-term follow up: If appropriate, researchers should consider obtaining consent to allow potential follow up through efficient means (such as routine data) as part of a separately funded study.

Rationale

Anorexia nervosa is an eating disorder and serious mental illness. People with the condition try to keep their weight as low as possible by either reducing their food intake or through excessive exercise, or by both. This can lead to malnutrition and serious illness. Anorexia nervosa has the highest mortality rate of all psychiatric illnesses.

A person with anorexia nervosa who is seriously malnourished is in a life-threatening state and may require inpatient refeeding. Refeeding is the provision of calories with the aim to restore physiological stability through weight gain.

However, there is risk associated with refeeding, namely refeeding syndrome. Refeeding syndrome encompasses the clinical and biochemical problems that may result from the reintroduction of nutrition rapidly to people who are malnourished and can be potentially fatal. Hypophosphatemia (a condition in which blood has a low level of phosphorus) is the most common symptom and is one of the earliest clinical indicators of the onset of refeeding syndrome. It has many effects including muscle weakness, biventricular cardiac failure and arrhythmias.

Therefore, refeeding has been approached with caution since refeeding syndrome was first identified over 80 years ago. This has meant that refeeding has begun at a lower calorie level with the aim to prevent refeeding syndrome occurring. In recent years, however, this approach to refeeding in people with anorexia nervosa who are malnourished has been questioned. It is suggested that lower calorie rates of refeeding are associated with initial weight loss, slow weight gain and prolonged hospital stays. This is characterised as underfeeding and may inadvertently prolong the acute risk of potentially life-threatening undernutrition. Evidence, especially in adolescents, suggests that refeeding for some people can begin at higher rates than previously thought without an increased risk of refeeding syndrome or other complications.

The Royal College of Psychiatrists has produced updated guidelines in the area: Medical Emergencies in Eating Disorders: Guidance on Recognition and Management (.PDF) (https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/college-reports/college-report-cr233-medical-emergencies-in-eating-disorders-(meed)-guidance.pdf?sfvrsn=2d327483_50). It sets out the existing evidence and highlights the clinical uncertainty about whether refeeding should

begin at a lower or higher calorie level. The guideline states that there is ‘an urgent need for a study of refeeding adults with anorexia nervosa in order to establish an evidence base for practice’.

The HTA Programme is interested in commissioning research to (a) evaluate whether it is feasible to deliver a trial of higher-calorie refeeding compared with lower-calorie refeeding in malnourished adults with anorexia nervosa and, if feasibility is successfully demonstrated, to (b) evaluate the clinical and cost-effectiveness of higher-calorie refeeding compared with lower-calorie refeeding.

Co-production, which ensures that the research demonstrates an equal partnership with service commissioners, providers and service users (or their advocates), should be embedded throughout the life cycle of the project from application to completion. Applicants may wish to consult the NIHR Learning for Involvement guidance on co-producing research (https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.learningforinvolvement.org.uk%2F%3Fopportunity%3Dnihr-guidance-on-co-producing-a-research-project&data=04%7C01%7CS.J.Gray%40soton.ac.uk%7C813a2b67fa444d547a7608d9af2cbf34%7C4a5378f929f44d3ebe89669d03ada9d8%7C0%7C0%7C637733428978529353%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=APPbADOt6gMB51qVmESLwjifidu%2FBw4mjywvmt7vCbM%3D&reserved=0).

Additional commissioning brief background information

A background document is available that provides further information to support applicants for this funding opportunity. It is intended to summarise what prompted the opportunity and the existing evidence base, including relevant work from the HTA and wider NIHR research portfolio. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field. If you would like a copy please email htaresearchers@nihr.ac.uk (mailto:htaresearchers@nihr.ac.uk).

Application guidance

Please read our Domestic Outline Application guidance (https://www.nihr.ac.uk/research-funding/application-support/guidance/domestic-programmes-outline-application-guidance) to help you complete all aspects of your application. You must read this alongside the information below, which details specific requirements our HTA Programme looks for in applications. You can also check our HTA Programme page (https://www.nihr.ac.uk/research-funding/funding-programmes/health-technology-assessment) for details about the Programme's scope and remit.

Research Plan

Write a maximum of five A4 pages for your Research Plan. This should include the background, rationale and all figures. When reviewing applications, we will not consider any additional information over this five page limit. Please include the following when writing your Research Plan.

Methodology/plan

Include the below detail in your methodology/plan:

Project design and methods

The research question

Please provide a concise statement of your proposed research including how it fits our HTA Programme remit.

You should include a clear explanation of the main (single) research question phrased in PICO terms where applicable to your study type:

- **Population:** NHS (or social care) target population i.e. real patients
- **Intervention:** A technology that is or could be used now in the NHS or social care. You may wish to refer to the Template for Intervention Description and Replication (TIDieR) guidance (http://www.tidierguide.org/)
- **Comparator:** Usually the next best treatment, but could be placebo
- **Outcome:** Patient/service user centred, leading to effectiveness and cost-effectiveness

For some funding opportunities, much of this information will be detailed in the research specification. In this case, you should only provide any relevant additional information not already captured in the research specification. If you wish to propose a study that does not meet one or more of the requirements set out in the research specification, please use this section to explain the reasons for your approach.

Summarise your project plan plus any additional points required to support statements made in previous sections of your application. Include any key references required to justify them (for example, the use of particular outcome measures or methods of analysis).

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health care services?

It is essential that you clearly identify the health and care need your research meets or contributes to. Please outline the anticipated value or contribution your study will provide. You must justify that this unmet need is a high priority to the NHS, social care or those who use these services. Your justification should be proportionate to the level of funding you are asking for. In some cases, substantive justification will be needed to prove your research is in an area of major importance. This includes detailing what support there is for this work from relevant clinical and patient communities.

Design

Dependent on the nature of the research you are undertaking, give a brief statement on the study design you will use, including:

- for primary research, state the health or care service setting(s) in which the study will occur. For example, general practice, hospital outpatients, ambulance service users, social care
- for secondary research or modelling, please explain the criteria applied to assess the quality and relevance of studies identified by the search strategy. Explain how these will be decided if these are not yet known

We welcome innovative methods that offer substantial benefits. If you plan to use a complex methodology, for example, Bayesian and model-based designs, you should justify this over a more standard approach. Benefits could include showing that the statistical properties are superior, or that the resources required are lower. You should also demonstrate that you have appropriate expertise within the research team to implement the approach.

What is the evidence that the intervention is ready for HTA evaluation?

For some commissioned funding opportunities, we will have already reviewed existing evidence to inform the research specification. In this case please ensure you meet the requirements in the research specification.

For researcher-led applications and commissioned funding opportunities with a broader scope, we require evidence that the intervention is ready for HTA evaluation (https://www.nihr.ac.uk/intervention-ready-hta-researcher-led-evaluation).

You should present and reference relevant high-quality evidence synthesis such as systematic reviews, modelling studies and meta-analyses. Where no such published evidence synthesis exists, you are expected to undertake an appropriate review of the currently available evidence. You should do this using a predetermined and described methodology that systematically identifies, critically appraises and then synthesises the available evidence, and then present a summary of these findings in your proposal.

You should propose valid and reliable methods for identifying and selecting relevant material, assessing its quality and synthesising the results. See the NHS Centre for Reviews and Dissemination guidance (https://www.york.ac.uk/crd/guidance/) for guidance on choosing appropriate methods.

If you are undertaking systematic reviews, please note our NIHR commitment to register these in the PROSPERO (https://www.crd.york.ac.uk/prospero/) database. PROSPERO was developed by our NIHR's Centre for Reviews and Dissemination (CRD). It is the first online facility to register systematic reviews for research about health and social care from all around the world. Access is completely free and open to the public. PROSPERO registration is a condition of NIHR funding for eligible systematic reviews.

If your proposed study builds on previous work then the results of the previous study must be available to the Funding Committee before an application will be considered. Please reference the published results. If not yet published, the committee may ask to see the results, along with evidence of acceptance for publication, to demonstrate that peer review has taken place.

Further to the guidance in the 'Background and rationale' section of the Research Plan, please justify the clinical importance of your proposed study to patients and the public, and outline the anticipated value or contribution the study will provide to clinical practice now and in future. You must justify that this unmet need is a high priority to the NHS, social care or those who use these services. Your justification should be proportionate to the level of funding you are asking for. In some cases, substantive justification will be needed to prove your research is in an area of major importance. This includes detailing what support there is for this work from relevant clinical and patient communities. In addition, please consider how your proposed intervention could be implemented across the wider NHS or social care settings.

Target population and inclusion/exclusion criteria

Clearly define the population from which the study sample receives the health technology concerned (or the control intervention where appropriate). For example, women over 60, people with a learning disability, people with advanced cancer. Please provide an

explanation of the inclusion/exclusion criteria.

Health technologies being assessed

Give a clear definition of the health technology to be assessed. The purpose of HTA is to assess the value of a health technology compared to best alternatives or where none exists, against no intervention. Where there are established alternative technologies, these should also be defined. Where the technology is subject to rapid change, you should include details of how this will be dealt with.

Measurement of costs and outcomes

Not all HTA studies require full economic evaluations. When considering including a cost-effectiveness analysis, you should carefully describe what this will add to the study. Where an economic component is proposed, you should aim to use the simplest approach, or fully justify where more complex methodologies are needed. You should justify the choice of outcome measures where a legitimate choice exists between alternatives. If your study includes a health economic component, state from what perspective costs and benefits will be considered, and (briefly) how these will be collected. Where established core outcomes exist, you should include these in the list of outcomes unless there is good reason to do otherwise. Please see the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website (https://www.comet-initiative.org/) to identify whether Core Outcomes have been established.

Longer-term follow-up

You should consider obtaining consent from participants to allow you to follow-up with them in the future. This would be through efficient means (such as routine data) as part of a separately funded study. You should therefore consider building in provision for a mechanism to facilitate longer-term follow-up beyond the life of the main study, including obtaining consent for this from participants at study entry.

Sample size

State the required sample size, giving details of the estimated effect size, power and/or precision employed in the calculation. You must provide this information so the Funding Committee can replicate the calculation and understand the assumptions made.

Difference between current and planned care pathways

Please define the current standard care pathway and how this differs from the trial arms.

Diagnostics and imaging

You should justify where you consider improvements in diagnostic accuracy to be relevant. 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 management and outcomes. You should also assess changes in other resources (particularly other subsequent therapies) used as a result of changes in diagnostic methods.

Dissemination

Our key concern is to ensure that projects funded by the HTA Programme are designed from the outset to produce useful, timely and relevant research findings which impact practice.

Studies within a trial or review (SWATs/SWARs)

You may apply for up to £30,000 funding to evaluate alternative ways of managing studies and how researchers can effectively engage with key stakeholders to promote the uptake and use of the evidence generated. This may be completed as part of your main study. Any methodological sub-study proposed should represent a very minor element of a larger study and must not undermine the delivery of the main study. There are some examples on the Northern Ireland Hubs for Trials Methodology Research web pages (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/).

You are also encouraged to review the work of Trial Forge (https://www.nihr.ac.uk/trial-forge-additional-guidance). Where there are already a number of SWATs answering the same or similar question, substantial additional justification would be needed. You may want to consider collaborations with groups able to carry out methodological work, for example around such issues as evaluating sustainability outcomes for trials. SWATs/SWARs may not all be powered to provide meaningful outcomes but will be useful for meta-analysis and you should consider using protocols published on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/ApplicationForms/). If you wish to include a SWAT/SWAR in your study, you should indicate that you intend to do so in your Outline Application. There is no need to provide a detailed description of the SWAT/SWAR at this stage.

Multiple long-term conditions - studies within a project

We encourage you to consider multiple long-term conditions (MLTC) studies within your project. This is to further understanding of MLTC, and improve knowledge on the best methods and processes for incorporating MLTC research questions into complex projects

(including clinical trials) in health, social care and public health. You can propose an embedded study within a project (SWAP) which would support this. The study would be short and efficient, with findings put into the public domain as soon as they are available, as an interim output. A SWAP will be a small part of the overall application and should be costed at no more than £30,000 to include all dissemination and publication associated with the SWAP. You are not required to give a detailed description of the SWAP at this stage.

Mechanistic research

We will support the collection of samples and data, where the HTA study provides an opportunity for valuable, hypothesis-testing research into the 'mechanism of action' of the intervention. The cost of sample collection and storage must be made clear in your application and must be modest in scale. Unless otherwise specified, any mechanistic work must be funded separately. You should note where there are plans to apply for and undertake the associated mechanistic study, for example via an application to the MRC-NIHR Efficacy and Mechanism Evaluation (EME) Programme. Any mechanistic work must not have a detrimental effect on the main study.

Timeline and milestones

Project timetables including recruitment rate

Indicate the anticipated duration of the study. Pay particular attention to the expected recruitment rate and justify your estimate. Outline the main stages of your proposed project including regulatory steps, team recruitment, patient recruitment, and the expected duration of each.

Study management

Expertise in your team

The team should be multidisciplinary and include relevant expertise in the clinical area concerned. They should have expertise in performing evidence synthesis and (where appropriate) other areas. For example, experience in operational research, being a patient and public involvement (PPI) Lead, being a public voice with lived experience, a health economist or statistician.

For commissioned topics, we strongly discourage the practice of the same co-applicant joining more than one competing team, other than in unusual circumstances (for example, a lead from a named charity or a unique national expert in a condition).

For such exceptions, each application needs to state the case as to why the same person is included. The shared co-applicant should not divulge application details between teams, and both teams should acknowledge in their application that they are aware of the situation, and that study details have not been shared.

Clinical Trials Unit involvement

We advise that studies involving a clinical trial have engaged with an accredited Clinical Trials Unit (CTU) listed on the UKCRC CTU Network (https://ukcrc-ctu.org.uk/). Note that you must provide a letter of CTU support with all Full Applications involving a clinical trial. If you are designing or undertaking clinical trials, we encourage you to consult the Clinical Trials Toolkit (https://www.ct-toolkit.ac.uk/).

Ethics/regulatory approvals

See the HRA website (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/) for guidance on the application process for ethical and other approvals. This process may vary depending where you are based in the UK. The HRA approval page (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/) provides more information.

If you are using patient information from an existing database, please ensure you have consent or that appropriate exemptions are in place. Approval to use confidential patient information without consent must be requested from the HRA who make decisions with advice from the Confidentiality Advisory Group (CAG) (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/confidentiality-advisory-group/).

To take advantage of the growing utility of routine data, we encourage you to consider asking participants to consent to long-term follow-up. That is, beyond the outcomes of the HTA study where appropriate.

See the UK policy framework for health and social care research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/) for a summary of the responsibilities of key research stakeholders.

Medicines and Healthcare products Regulatory Agency (MHRA) considerations

The MHRA (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency) can provide guidance on the regulations that apply to your study. If you are

planning a study on a medicine used outside its licensed indication, dose, or formulation, we encourage you to contact the Medicines Repurposing Programme (https://www.england.nhs.uk/medicines-2/medicines-repurposing-programme/) for support and advice before submitting your application.

Application process

Find out how to apply for this funding opportunity and what you need to do to get your application ready.

How to apply

When you are ready to apply, you will need to log in to our application system to apply (https://awardsmanagement.nihr.ac.uk/s_Login.jsp?dest=/Apps/app_viewopportunity.jsp%3Fappid%3D105112%26nextlevel%3D1%26opportunityid%3D10082504). This funding opportunity is on our new Awards Management System and you will need to create a new account to apply.

The closing date is 2 April 2025 at 1pm. Applications received after 1pm on the closing date will not be considered.

Please read the following guidance before submitting an application:

- all the application guidance detailed in the 'application guidance' section in this funding opportunity

Download application form template

You can download a Word document template of the application form below. Please use this template as a guide only, to help you prepare your application. For example, to see how many characters are accepted in each section and to see how information in the form is laid out. Please do not try to use this as an application form; it cannot be submitted as an application. You must submit your application online via our Awards Management System.

(/media/24286/download/)
domestic-outline-application-form-template.docx

DOCX

Last updated: 27 November 2024

Download document (27.86 KB)

Research inclusion and reasonable adjustments

At NIHR we are committed to creating a diverse and inclusive culture (https://www.nihr.ac.uk/about-us/who-we-are/research-inclusion). We encourage applications from people from all backgrounds and communities bringing diverse skills and experiences. If you need any reasonable adjustments throughout the application process, please contact the programme team via the information in the Contact Details tab.

Research Support Service

Got a research idea and not sure how to turn it into a funding application? The free NIHR Research Support Service (RSS) (/support-and-services/research-support-service) supports researchers in England to apply for funding. It can help you develop and deliver clinical and applied health, social care and public health research post award.

- For help with your application contact HTACommissioning@nihr.ac.uk (mailto:HTACommissioning@nihr.ac.uk)
- For more information about the funding Programme, visit the HTA Page (/research-funding/funding-programmes/health-technology-assessment)
- Got a research idea and not sure how to turn it into a funding application? The free NIHR Research Support Service (RSS) supports researchers in England to apply for funding, and to develop and deliver clinical and applied health, social care and public health research post award. Find out how the RSS can help you (https://www.nihr.ac.uk/explore-nihr/support/research-support-service/).