CLINICAL TRIALS GUIDE FOR TRAINEES
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Clinical trials, compared to observational studies, are considered by many to be the gold standard method for evaluation of healthcare interventions. They contribute significantly to relevant research evidence developed by the National Institute for Health Research (NIHR) to support the NHS in England and other care providers. However, clinical trials are complex and many researchers, particularly those in the early stages of their career, find it challenging to know where to start, either to contribute to or lead a trial.

After conducting an internal report on trainee engagement in clinical trials, the NIHR Trainees Coordinating Centre began a project to develop a source of information to support individuals interested in pursuing a research career that involves the delivery of clinical trials.

Version 1 of this booklet, released in 2015, was the outcome of the first stage of the project which was to determine which questions aspiring trialists need answering ahead of starting their journeys into clinical trials.

This latest version (version 2) contains additional guidance for people looking to develop their career in clinical trials, developed by an NIHR task and finish group set up to consider how to increase capacity and capability in clinical trials. This latest version also contains case studies both of trainees who have started to develop their career in clinical trials and also case studies from CTUs showing how they can provide support to trainees.

If you have any suggestions or feedback then please email tcc@nihr.ac.uk or tweet us @NIHR_trainees
We would like to thank the following people for assisting the NIHR Trainees Coordinating Centre in bringing this guide together:

Liz Tremain  
Senior Programme Manager, NIHR Evaluation Trials and Studies Coordinating Centre

Professor Lelia Duley  
Director, Nottingham Clinical Trials Unit

Professor Lesley Stewart  
Director, Centre for Reviews and Dissemination, York

Professor Andrew Fisher  
Associate Dean for Clinical Academic Training Newcastle University

Dr Wendy Baird  
Director, NIHR Research Design Service for Yorkshire and the Humber

Dr Maria Bryant  
Leeds Clinical Trials Unit

Dr Duncan Harding  
NIHR Clinical Lecturer, IoP, King’s College London

Dr Carsten Flohr  
NIHR Clinician Scientist, King’s College London

Dr Angelos Kolias  
Specialty Registrar Neurosurgery, University of Cambridge

NIHR Clinical Trials Training Task and Finish Group

We hope you find this information helpful and we wish you luck in your future trials!

The NIHR Trainees Coordinating Centre.
2. GENERAL INFORMATION

What exactly is meant by the term ‘clinical trial’?

A clinical trial is a research project that compares two or more treatments in patients with a particular condition or at risk of a condition to help generate high quality evidence about which is the more effective treatment or preventative strategy. The treatment being investigated in a clinical trial can be a medicinal product, a procedure, a device or another type of therapeutic intervention. Clinical trials are an essential part of the process of evidenced based practice and can help guide treatment decisions for both health care professionals and patients. Clinical trials are an important part of the pathway by which new medicinal products can obtain a licence from MHRA and become available for use as a new treatment in patients.

I like the idea of becoming involved in clinical trials, but don’t know how to go about this. Where do I start?

Clinical trials are performed widely across the NHS and the Research and Development Department in your local NHS Trust will have a record of all the clinical trials active in your hospital. Many trials are also registered on national and international databases that are searchable and can identify trials in specific diseases or using specific treatments. These include the NIHR research network databases, Clinical Trials.gov, UK Clinical Trials Gateway and EudraCT.

Many clinical trials, especially those involving a new medicinal product or involving multiple sites, are supervised by a Clinical Trials Unit (CTU) or a Contract Research Organisation. Your local registered CTU will also be a good point of contact about clinical trials being performed in your area.
What is generally involved in conducting a clinical trial?

A clinical trial should be considered when there is uncertainty as to which of a range of treatment options or preventative strategies is more effective. A team of investigators are responsible for conducting a clinical trial and this requires meticulous planning.

Once the case for a new clinical trial has been made on medical, ethical and financial grounds then the trial needs to be designed so that it will provide the highest possible quality of evidence to guide future decision making. Trial design is a multi-disciplinary activity involving input from clinicians, trial methodologists, pharmacists, statisticians and health economists among others.

After the clinical trial is designed, the funding to pay for the trial to be conducted must be identified either from industry, who may fund a clinical trial as part of the development pathway for a new medicinal product, device or technology or from a research funding body such as NIHR or Medical Research Council or from a charity such as Cancer Research UK or the British Heart Foundation. After funding is secured, then all the necessary permissions such as research ethics approval and NHS research governance approval must be sought.

Training on the legal responsibilities when conducting a trial can be provided locally as a Good Clinical Practice (GCP) course which is offered by your local NIHR Clinical Research Network.
How will I know whether or not a clinical trial is appropriate for my research?

Before embarking on a clinical trial it is important to establish whether a new trial is indeed needed. You should check what research has already been done. Are there existing trials that may provide enough evidence to answer the question that you wish to address?

The NIHR is committed to avoiding waste in research and unjustified duplication of a trial is unlikely to be funded. The NIHR and other research funders recommend that all clinical trials should start with a systematic review of the existing research evidence. This may reveal that there is already sufficient high-quality research evidence to answer your research question (in which case you will need to think of a new trial or project) or provide sound information to justify your research, and potentially help with your trial design.

If a clinical trial isn’t appropriate, what are my other options?

Clinical trials are not always the most appropriate option to further your research and to support the development and evaluation of new treatments. A pilot study to assess the feasibility of conducting a clinical trial is often needed. The pilot study will allow the team of investigators to determine the likely difficulties in performing a full clinical trial and also inform the calculations on sample sizes in a full clinical trial to be done.

An observational study may be a more appropriate option if there is uncertainty about the most robust endpoints to use in a clinical trial, or if the mechanism of a potential new treatment has not been established.
Claire Mitchell is a Speech and Language Therapist. Claire was inspired to get involved in research after returning from maternity leave to discover there was a particular area where nothing had changed in terms of the evidence base in 20 years. Claire felt that something needed to be done. She is now leading a project looking into technology and how it may be able to help patients after they have a stroke.

“My NIHR award has been a great opportunity to learn the background to running a trial and understanding all that goes with that”

Claire Mitchell
NIHR Doctoral Research Fellow
What would be a realistic timescale for a clinical trial and does this differ at all?

The time required to design a clinical trial, produce the detailed trial protocol and secure all permissions is substantial and can take 6-12 months to complete.

The time required to perform the clinical trial will vary widely and will depend on the sample sizes needed, the frequency by which participants are recruited and the follow up period for each participant in the study.

How many projects should I become involved in?

If new to clinical trials, it is best to get involved in one clinical trial initially and fully understand the processes involved in more detail.

What pitfalls should I be aware of in general?

By working with an experienced CTU and experienced trial methodologists then the risk of pitfalls can be reduced. However, common pitfalls include underestimating the time it takes to develop the trial protocol and secure all the permissions before starting.

Failing to recruit participants in an appropriate time-frame is also a significant pitfall. There is a risk in over predicting the ease by which specific groups of patients will be willing to participate and this can lead to unrealistic milestones being set.

Careful monitoring for serious adverse events is essential when conducting a clinical trial. If these events occur they will be reviewed by the research ethics committee and by an independent data monitoring committee who have the power to terminate a study early if there is potential that the intervention being assessed is causing harm.
The following simple checklist may help you decide whether a clinical trial is appropriate for your research:

Step 1 – establish whether a relevant systematic review already exists
✓ If yes, and this resolves the clinical uncertainty – stop;
✓ If yes, and it demonstrates continued uncertainty – continue to design and justify your trial, using information from the systematic review as part of your justification;
✓ If yes, but the review is out of date, or of poor quality – consider updating the review;
✗ If no – consider doing a systematic review.

Step 2 – establish whether relevant clinical trials exist
Are there already clinical trials that address your research question;
✗ If no, continue to design and justify your trial;
✓ If yes, but there is clearly insufficient evidence to answer the clinical question robustly e.g. a single trial with uncertain results - use this information to justify the need for and inform the design of your trial;
✓ If yes, consider carrying out the systematic review as a first step.

Even if similar reviews or trials exist, if these are in a different context or setting, or address a slightly different question, your trial may still be relevant – but it will be important to be clear why it is different and still needed.

When searching for systematic reviews or clinical trials it is helpful to enlist the help or advice of a trained information specialist or medical librarian.

Useful places to search:

Completed systematic reviews:
www.cochranelibrary.com/ and www.crd.york.ac.uk/CRDWeb

ongoing systematic reviews:
www.crd.york.ac.uk/PROSPERO/

ongoing clinical trials:
NIHR spends a large proportion of its research programme budget on clinical trials. The importance of clinical trials to the NIHR means that it is very keen to attract and develop future clinical trial leaders. NIHR research training awards support outstanding individuals to become health research leaders of the future and supporting people who will lead NIHR funded trials is very much within this remit. The schematic below highlights how you may utilise NIHR’s suite of research training awards to start or further your career in clinical trials.

**New to clinical trials?**

For pre-doctoral applicants:
A Doctoral Research Fellowship focussed on a trials relevant topic or small trial/feasibility study.

For post-doctoral applicants:
A Transitional Research Fellowship to undertake an intense period of Clinical Trials Training.

**Further your trials experience.**

For existing NIHR trainees:
A Clinical Trials Fellowship to gain further broad training in clinical trials in partnership with CTU.

For post-doctoral applicants:
A range of post-doctoral level training awards which can be utilised for those interested in furthering their clinical trials career.

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**3. FELLOWSHIPS AND CLINICAL TRIALS**

Do clinical trials fit within the remit of NIHR Research Training Awards?

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“Before I came into the NIHR I had very limited experience of trials. The award has given me a personal training programme that’s allowed me to learn all about them”.

Barney Dunn
NIHR Career Development Fellow

Barney is a Clinical Psychologist and is passionate about trying to make a difference in mental health care in the NHS. Barney’s research is trying to improve the outcomes for psychological therapies for depression by developing and trialling a new treatment.
What aspects of a clinical trial can realistically be included within a Fellowship application to NIHR? Does this change depending on the level of award I apply for?

Applicants do need to consider:

- the type (e.g. clinical trial of investigational medicinal product (CTIMP), trial of surgical intervention or trial of complex intervention);
- the scope (single or multi-centre);
- feasibility / pilot trial (http://www.nets.nihr.ac.uk/glossary?result_1655_result_page=F);
- phase of trial (I to IV), and
- risk level of the trial (see http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Submittinganotificationforatrial/index.htm in respect of CTIMPs)

Applicants should also ensure it is commensurate with the level of award and experience of the applicant. For example, we would not normally expect a doctoral level applicant to propose leading a multi-centre randomised controlled trial of an investigational medicinal product. Fellowship applications, especially at doctoral and early post-doctoral level, will tend to focus on feasibility and pilot trials or may form a distinct add-on to an existing trial (in this case it must be clear the trial is a distinct, standalone piece of work and the role of the applicant must be clear).

Applicants are strongly encouraged to read the additional guidance from page 46, which outlines the expectations NIHR has for what a research training award based around clinical trials should deliver, and should be read in conjunction with guidance specific to the scheme you are applying to.
What is the difference between running a clinical trial in an NIHR Fellowship and an NIHR project grant?

It is very important that applicants keep in mind that the proposed research project in a Fellowship application is a vehicle for training and this needs to be clearly demonstrated as part of the application.

Applications for a fellowship can't just look like a project grant application. Applicants should also consider the feasibility of the trial within the scope of a fellowship award. NIHR research training awards are personal fellowships and not project or programme grants; therefore awards will not be extended to allow completion of a trial. Please bear in mind the lead in time for clinical trial set-up vis-à-vis the time available within the course of a fellowship.

Run-in time for drug and placebo procurement, manufacture and packaging for CTIMPs and the fact these activities must be completed, before regulatory approval can be sought, must be taken into account when planning the fellowship schedule and completing the application form. Regulatory, ethical and R&D approval can take several months and appropriate advice on the processes and timelines should be sought from the outset.

How do I move from hypothesis-generating to clinical trials hypothesis-testing under an NIHR funded career pathway?

There are a number of pathways, depending on a person’s experience and the sort of trial needed. This might be a doctoral fellowship, for a hypothesis answered within a small single centre trial, or the doctoral/postdoctoral fellowship might be a pilot/feasibility study, then a later fellowship might support a full trial. If in doubt, please contact your local Clinical Trials Unit, Research Design Service or the NIHR Trainees Coordinating Centre.
“Having a basic understanding of clinical trials is key for anybody who is involved, not only in research, but seeing patients in day-to-day clinical practice”.

Carsten Flohr
NIHR Career Development Fellow

Carsten is a specialised clinician in paediatric dermatology and runs a research unit that specialises in population-based dermatology research. Carsten is running a national clinical trial across 14 centres for children with severe atopic eczema.
What parts do I need to seek approvals for in my research? Where do I obtain approval from?

On 31 March 2016, Health Research Authority (HRA) Approval became the route for applying for approval to conduct research in the NHS in England. HRA Approval brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK research ethics service. Further information is available on the HRA website: http://www.hra.nhs.uk/about-the-hra/our-plans-and-projects/assessment-approval/

HRA Approval removes the need for NHS permission to be issued by each participating organisation and replaces the local R&D approval process previously delivered through NIHR CSP. As a result the NIHR CSP system was withdrawn from service on 5 August 2016, following its closure to new applications in March.

HRA Approval will provide a single approval for project based research in the NHS in England.

Local organisations will now concentrate on assessing, arranging and confirming that they have the capacity and capability to participate in the study.

If your study is eligible for Clinical Research Network (CRN) support, CRN will support you with setting up and delivering your study within the NHS through the Study Support Service (https://www.crn.nihr.ac.uk/can-help/study-support-service/).

Please ensure that you apply to the CRN as early as possible, ideally before submitting any other regulatory approvals, including your application for HRA Approval, using the Portfolio Application Form https://www.myresearchproject.org.uk/.

Is there a pathway I can follow in order to obtain regulatory approval? Where can I find out information on trial governance?

Comprehensive guidance on the support that the NIHR Clinical Research Network (CRN) can give to non-commercial researchers can be found here: http://www.nihr.ac.uk/funding-and-support/study-support-service/

The NIHR CRN workforce development team have developed Good Clinical Practice training which is free to researchers which may be useful for trainees. You can find out more at the following link: www.crn.nihr.ac.uk/learning-development/good-clinical-practice/
How much monitoring should I be doing?

Monitoring and governance information can be found within the HRA research community website:

www.hra.nhs.uk/research-community/during-your-research-project/

The monitoring of a clinical trial is usually done by the Clinical Trials Unit and/or the Sponsor institution.

How do I, and can I, publish the protocol for a clinical trial?

It is a condition of Research Ethic Committee (REC) favourable opinion that trials are registered:


In addition, many trial protocols are published in journals, such as the online BioMed Central (BMC) series.

Please note that trial registration is not quite the same as publication of the protocol. Open access journals will often publish trial protocols and they can also be made available on a study or unit website.

Further information on approvals and when they will be required can be found by using the Clinical Trials Toolkit route map:

www.ct-toolkit.ac.uk/routemap
3. THE CLINICAL ACADEMIC ROLE

There are many clinical trial designs and the exact type depends on your research question. The optimum design is the one that is least likely to incur bias and will have the best chance of answering your research question. For example, if the intervention under investigation is delivered in groups, it might be most appropriate to choose a cluster randomised trial. Alternatively, if you are testing a drug to treat a chronic disease, you are more likely to consider an individually randomised design. When considering trial ‘phase’, the most common phases in clinical trials are phase II trials, feasibility trials, pilot trials and phase III trials of effectiveness/efficacy.

The term ‘phase’ usually refers to I-V:
- I = first in man
- II = proof of concept/efficacy
- III-V = effectiveness
- Pilot or feasibility studies could be done for any phase of trial.

For further information, please see the following:


4. DESIGNS, TYPES AND PLANNING

What are the different types of trials?

There are many clinical trial designs and the exact type depends on your research question. The optimum design is the one that is least likely to incur bias and will have the best chance of answering your research question. For example, if the intervention under investigation is delivered in groups, it might be most appropriate to choose a cluster randomised trial. Alternatively, if you are testing a drug to treat a chronic disease, you are more likely to consider an individually randomised design. When considering trial ‘phase’, the most common phases in clinical trials are phase II trials, feasibility trials, pilot trials and phase III trials of effectiveness/efficacy.

The term ‘phase’ usually refers to I-V:
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- Pilot or feasibility studies could be done for any phase of trial.

For further information, please see the following:


I’ve heard other trainees talk about trial designs, what does this mean?

Trial designs incorporate many aspects to optimise the ability for teams to answer their research questions. The term can refer to all aspects of the study design and how it is implemented, including all methodological aspects and the patient pathway.

Commonly used designs in trials include:

Parallel group trials – groups or individuals randomised to one of two interventions (A or B) with outcomes compared at the final endpoint (either by comparing differences in a pre-specified primary outcome at a pre-specified time point, or by comparing the disease severity between baseline and follow-up).

Factorial trials – groups or individuals randomised to single treatments (A or B), or a combination of treatments (A and B). This design allows you to answer two or three questions at once (e.g. is treatment A more effective that treatment B / Is the combination of treatments better than a single treatment A etc.) and enables you to consider potential interactions.

Cross over trials – groups or individuals randomised to one of two treatments (A or B), followed by a wash-out period (not always needed) then switching of treatments (B or A). These are only possible in trials of chronic conditions; they are also carried out for other conditions; however whether or not this is useful is a different question.

Whilst the above gives a brief overview, it should not be taken that this is all that needs to be considered in study design.

For more information please go to:

www.ct-toolkit.ac.uk/routemap/trial-planning-and-design
How would I know which design to choose? What do I need to consider when choosing my design?

It is important to talk to people with expertise and experience in trial design and methods to help you design your study.

If you are involving a CTU, there will be experts here to support you. Otherwise, your supervisory or mentoring team should include someone with experience and/or expertise in trial design, and the your local Research Design Service will be able to provide additional advice. Trial statisticians are very important collaborators that can help with planning and designing your study.

Once you think you have chosen the best design, consider all of the ways that bias might be introduced in that design:

www.ct-toolkit.ac.uk/routemap/trial-planning-and-design.

How can I minimise the potential for bias in my clinical trial design?

Each type of possible bias should be considered and appropriate approaches/designs implemented, such as participation bias reduced by the recruitment methods (e.g. recruited by independent researchers/clinicians).

The following is a resource commonly used for systematic reviewers and may be useful for trialists.

http://handbook.cochrane.org/
Are there any study designs that can be used in situations where it wouldn’t be appropriate/feasible to conduct a clinical trial?

Trials are no longer restrictive and many innovative approaches and study designs are possible, even with the most complex of interventions.

When should a pilot study be performed before a clinical trial and what methods should be used in a pilot study?

For further information on what pilot and feasibility studies should include and what the definitions are for both, please see Additional guidance for applicants on page 46.

How do I go about developing my research question into a clinical trial proposal?

The following is a useful document for this issue:

3. THE CLINICAL ACADEMIC ROLE

Multi-site trials make results more generalizable to the population. They also increase the ability to recruit. Multi-centred trials require a different set of skills and expertise to single site studies and are often more challenging to conduct, e.g. more work getting sites to agree, set-up, approvals and monitoring.

From the point of view of the NIHR a trainee can lead a multi-centre study and it may be very beneficial for their training and development to do so, provided they have appropriate experience of clinical trials and the right support around them. Please be aware that there are both large multi-centre and small multi-centre studies; this is not a single entity.

Any decision about the role a trainee will have on a clinical trial and the size and scope of that trial should be taken in discussion with supervisors and/or mentors bearing in mind the scope of the research training award in which the trial will be included and the experience and expertise of the individual. For instance, a senior fellowship holder with significant clinical trials experience may well be very suitable to lead a multi-centred trial, whereas a doctoral level fellow with limited trial experienced would be more likely to focus on smaller scale/feasibility studies.

What are the advantages and disadvantages of a multi-centred trial?

Multi-site trials make results more generalizable to the population. They also increase the ability to recruit. Multi-centred trials require a different set of skills and expertise to single site studies and are often more challenging to conduct, e.g. more work getting sites to agree, set-up, approvals and monitoring.

Can NIHR trainees or fellows lead a multi-centred trial?

From the point of view of the NIHR a trainee can lead a multi-centre study and it may be very beneficial for their training and development to do so, provided they have appropriate experience of clinical trials and the right support around them. Please be aware that there are both large multi-centre and small multi-centre studies; this is not a single entity.

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“My NIHR Research Professorship has helped me in developing my career in clinical trials, but more importantly it has supported me to support a new group of future clinical trials leads”.

Nadine Foster
NIHR Research Professor

Nadine Foster is an NIHR Research Professor in Musculoskeletal Health in Primary Care and the Director of Keele Clinical Trials Unit. Nadine got the research bug back when she was a Physiotherapy student and wanted to find out why the treatments offered were being used as well as the evidence behind them. Nadine is involved in the full suite of randomised trials and leads and delivers a large portfolio of studies.
5. METHODOLOGIES

Where would I go to find help with analysing data produced by the trial?

Analysis plans are usually written by trial statisticians with input from the study team, and the data analysis is likewise conducted by the trial statistician. This is in part to ensure robust blinding to the study intervention throughout the trial. However, where a clinical trial forms part of a higher degree, especially where a pilot or feasibility study is conducted, it would be very suitable for the PhD student to be involved in the data analysis.

The level of input will depend on the level of the fellowship that you’re applying for and what can be requested in terms of the scheme. It is not recommended that fellows seek to do this on their own unless they have expertise in this area. Given that most applications will be for pilot or feasibility studies, most trainees will only be looking at descriptive analysis; however most will also involve sample size calculations, which will require input from an expert.

Where can I get statistical assistance, such as how to do a power calculation?

At the pre-funding application stage, this support can be sought either from the trials unit that you are collaborating with or from the Research Design Service.

What should I be looking out for when interpreting data from clinical trials?

The analysis plan (which should be written during the set-up period) should clearly indicate how data will be analysed and will state what the measure of efficacy/effectiveness will be. Collaboration with a statistician is essential for writing the analysis plan. Once the analysis is complete, interpretation of the data should involve the full trial team including all stakeholders. Involving patient and public involvement groups will help ensure a patient perspective in interpretation of the data.
6. TEAMS AND MANAGEMENT

Are there any managerial and/or structural frameworks available for managing a clinical trials team?

Things to bear in mind when managing a team are:

- make sure you choose the right people (provision of expertise and those conducting the research);
- ensure accountability (e.g. contracts);
- schedule meetings in advance;
- standing agenda items related to co-applicant involvement;
- publication strategy and plan in advance (linked to protocol)

For further information on clinical trials management, please follow these links:

www.ncbi.nlm.nih.gov/pmc/articles/PMC2917433/
What is public involvement in research?

INVOLVE defines public involvement in research as research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them.

The NIHR expects patients and the public to be actively involved in all stages of the research process from project design to disseminating the findings in any research it funds.

When using the term ‘public’ we include patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services. Whilst all of us are actual, former or indeed potential users of health and social care services, there is an important distinction to be made between the perspectives of the public and the perspectives of people who have a professional role in health and social care services.

For further information, please see Briefing Note 2 via the link at the end of this section.

Where do I start with patient and public involvement?

To help you plan and undertake public involvement in your research we suggest you consider the following points:

- involve people as early as possible;
- be clear with those you involve about what their role will be;
- be accessible;
- resource public involvement in research;
- offer training and support;
- clarify organisational responsibilities;
- document and record public involvement in your research.

You can find out more patient and public involvement at:

What are the practical issues regarding selection? Who should I involve and how do I find them?

In deciding who best to involve it is important to think about the knowledge and perspective that you are looking for from members of the public, and what support you are able to give to people who you plan to involve.

Even if your research is about informing practitioners about approaches to practice, the end user of the research will be the person receiving the practice. In some research projects you will want to consider involving both practitioners and members of the public.

Once you have considered who you would like to involve, you then need to think about how to make contact with them. Speak with colleagues and members of the public and ask for their views on how to find the people you want to involve. Allow time to make contact with organisations and individuals as finding people will nearly always take longer than you think.

For further information, please see Briefing Note 6 via the link at the end of this section.

For further information on PPI, including the full set of Briefing Notes for Researchers, please see the links below:

Briefing notes:
3. THE CLINICAL ACADEMIC ROLE

CTUs are specialist units which have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. They have the capability to provide specialist expert statistical, epidemiological and other methodological advice and coordination to undertake successful clinical trials. In addition, most CTUs will have expertise in the coordination of trials involving investigational medicinal products which must be conducted in compliance with the UK Regulations governing the conduct of clinical trials resulting from the EU Directive for Clinical Trials.

Units awarded UKCRC Registration are required to provide evidence to an international panel of experts of their capability to centrally coordinate multi-centre clinical trials (i.e. having overall responsibility for the design, development, recruitment, data management, publicity and analysis of a portfolio of trials), and that they have established robust systems to ensure conduct and delivery of clinical trials to the highest quality standards. More information on the UKCRC CTU Network and unit registration can be found at www.ukcrc-ctu.org.uk/

8. CLINICAL TRIALS UNITS

What does a Clinical Trials Unit (CTU) do?

CTUs are specialist units which have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. They have the capability to provide specialist expert statistical, epidemiological and other methodological advice and coordination to undertake successful clinical trials. In addition, most CTUs will have expertise in the coordination of trials involving investigational medicinal products which must be conducted in compliance with the UK Regulations governing the conduct of clinical trials resulting from the EU Directive for Clinical Trials.

Units awarded UKCRC Registration are required to provide evidence to an international panel of experts of their capability to centrally coordinate multi-centre clinical trials (i.e. having overall responsibility for the design, development, recruitment, data management, publicity and analysis of a portfolio of trials), and that they have established robust systems to ensure conduct and delivery of clinical trials to the highest quality standards. More information on the UKCRC CTU Network and unit registration can be found at www.ukcrc-ctu.org.uk/
In what ways will a CTU help me with my clinical trial?

CTUs collaborate with you to play a key role in providing the dedicated expertise and support necessary for the design, development, management, analysis and publication of high quality clinical trials. Registered CTUs will usually work with the Chief Investigator on the following:

Coordination and preparation of the grant application including;

- Trial development (including the question identification and appropriate design)
- Systematic reviews (when appropriate)
- Trial costing and staff planning
- Discussion with disciplines required for different trial components e.g. quality of life, health economics, associated translational research
- Sub-study development. Communication with research networks regarding feasibility and levels of interest
- Conduct of the trial including;
- Regulatory and governance issues
- Negotiation with international collaborators and/or industry (if applicable)
- Management of funded trials
- Protocol development and Case Report Forms (CRFs) design
- Liaising with potential centres and sites, identifying and initiating participating centres, and maintaining good communications throughout to deliver required patient identification and recruitment
- Trial set-up and permissions (e.g. ethics, MHRA etc.)
- Central coordination and management of essential trial documents and patient data
- Data monitoring
- Analysis and publication including;
- Interim and final analyses
- Report preparation (e.g. for funding bodies, MHRA, Data Monitoring Committee, Trial Steering Committee)
How do I gain access to a Clinical Trials Unit?

The UKCRC CTU Network contains a variety of information on registered units, including a resource finder. You are able to search for CTUs that are interested in supporting fellowships and other research training award applications and also search based on the disease area, study type and methodological expertise of the CTU. The resource finder is available to use at:

www.ukcrc-ctu.org.uk/search/custom.asp?id=468

The NIHR recognises the important and crucial role played by CTUs in helping the design, development and delivery of quality research projects, and provides NIHR CTU Support Funding to selected units in England to support their NIHR activity. A list of units receiving funding and interested in collaborating on NIHR research is available from www.nets.nihr.ac.uk/programmes/ctu

If you are interested in working with a CTU, you should contact them as early as possible in the process. Ideally, this should be at least three months before a research grant application deadline (although many units prefer longer than this for open calls) in order to provide adequate time to schedule the work required and ensure the CTU is able to offer the full benefit of its experience and knowledge from the initial stages of study development. You will need to provide the CTU with information about your study and your requirements. Some CTUs will have their own collaboration request form.

A short video outlining the support a CTU can provide is available to view here: ‘The role of Clinical Trials Units in developing an NIHR funding application’:

https://www.youtube.com/watch?v=QvGaGEHgwXg&feature=youtu.be.
“My placement at a Clinical Trials Unit gave me a bird’s eye view of clinical trials from beginning to end”.

Matthew Hyde
NIHR Transitional Research Fellow

Matthew Hyde’s background is in animal science and his research is looking into the way that birth can be a cue for later life development. Matthew used an NIHR Transitional Research Fellowship to take his research into a human clinical setting and build his skills in clinical research and clinical trials specifically.
What support does your CTU offer to people applying for fellowships and other research training awards?

Meeting or phone call with KCTU statistician and KCTU operations director to discuss proposal. All are directed to RDS for additional support. Supervisors need to have appropriate experience – in some cases, where statistics is complex and beyond proposed supervisors capabilities, they are advised to simplify project or add a statistician supervisor.

What models of support does your CTU provide to those undertaking a fellowship or other research training award?

Model is for candidate to remain physically in their academic department throughout fellowship.

For pre-doctoral fellowships, regular meetings (quarterly) with statistician +/- operational staff is offered to provide guidance on processes (protocol, eCRF, data management plan, monitoring plan, SAP development) and project planning but the expectation is that student will analyse project. Data is typically managed via spreadsheets. Randomisation service is offered.

For post-doctoral fellowships, the decision on whether support is offered on an advisory basis only or if analysis is taken on by the KCTU statisticians or economists depends on the objectives of the fellowship. eCRF may be offered, depending on size and complexity of planned dataset. Randomisation service is offered.

Costed support with trial management is not offered but students can access twice monthly free KCTU advisory sessions run by KCTU operational staff and are actively encouraged to join the KCTU trial managers and data managers network, which runs lunchtime seminars and networking events every 6 weeks and which is free to attend.
Are there any other ways that your CTU supports individuals looking to further their career as a clinical trialist?

KCTU offers a bursary scheme for KCL staff, funding 50% of the LSHTM fees to undertake a certificate in clinical trials by distance learning. 17 staff will be studying in 2016-2017.

An online training program for trials staff is available at www.ctu.co.uk and courses are being added continuously – this is free to staff and students.

In your opinion why is it important for trainees to work with a CTU, where possible, when undertaking research training relevant to clinical trials?

In order to adopt best practice standards and understand the rationale for developing and delivering a methodologically and clinically robust study protocol.
What support does your CTU offer to people applying for fellowships and other research training awards?

All people applying for fellowships have a research supervisor of a relevant discipline who is based at PRIMENT. In addition Priment offers support with the following:

- Research design
- Writing research proposals
- Statistical and health economic advice
- Advice about funding streams
- Assistance with costings

Applicants are also welcome to present their research ideas to our Research Proposal Seminars which are held monthly.

What models of support does your CTU provide to those undertaking a fellowship or other research training award?

Priment provides those undertaking a fellowships a model of support that encompasses the areas of methodology, statistics, health economics and operations. Key areas for support are:

- Statistical design and analysis
- Health economics
- Data management
- Writing trial protocols and related documentation Handling and managing budgets
- Patient randomisation
- Trial operational support
- Trainees work with Triallists to see how proposals for funding are developed
- Opportunities to review other proposals to gain a broad exposure to clinical trials
- Advice and support in PPI in research
- Opportunity to attend and present at the Priment Methodology and Statistics Seminar
- Opportunity to work closely with statisticians, health economists, trialists and the operations team
Are there any other ways that your CTU supports individuals looking to further their career as a clinical trialist?

At Priment CTU we have a number of experienced trialists who are able to provide support and guidance to trainees and other earlier on in their career. As Priment is part of UCL's Institute of Clinical Trials and Methodology individuals have the opportunity to undertake short courses in trial conduct and methodology.

In your opinion why is it important for trainees to work with a CTU, where possible, when undertaking research training relevant to clinical trials?

Working with a CTU provides trainees the opportunity to work with all disciplines involved in clinical trials from methodologists to operational staff. In this way they have a better understanding for the importance of all the various aspects of trials. They are able to access expertise in areas which are often difficult to access outside a CTU such as health economics, statistics and data management.
What support does your CTU offer to people applying for fellowships and other research training awards?

We provide guidance and support with the completion of applications, including review and feedback on applications and helping candidates understand the application process. Specifically this may entail a meeting(s) with members of the CTU to discuss the interests and experience of the applicant and how the NCTU can support their career development. Fellowships we support include Research Methods and Clinical Trials Fellowships, Doctoral or Post-doctoral awards that include a feasibility trial or research relating to trials methodology, and more senior fellowships that include a full clinical trial as part of the award. We provide input to research design, formulate with each applicant a programme of training that matches their requirements, and offer formal supervision for research degrees if appropriate.

What models of support does your CTU provide to those undertaking a fellowship or other research training award?

This depends on the award.

For example, for CT Fellowships we provide:

- Experiential learning – development of a tailored work plan to meet individual needs involving participating in a range of trial and unit wide activities
- Coaching/mentoring – fellows are assigned an academic supervisor and senior trial management supervisor to lead their work plan and support their time in the unit
- Reflective practice – through regular meetings with their academic and trial leads to review progress and identify challenges, achievements and knowledge gaps

For senior fellowships that include funding for a full clinical trial, we provide senior individual(s) who mentor the fellow and are part of a steering group for the fellowship, as well as full support for the clinical trial.
Are there any other ways that your CTU supports individuals looking to further their career as a clinical trialist?

We are always open to receiving collaboration proposals for clinical trials. For individuals still developing their career as a clinical trialist, we may support them to apply as co-CI so they can be appropriately mentored in the skills required to be a successful CI. We have a seminar programme open to anyone, and we are currently developing a programme of short courses in research methods for clinical trials.

In your opinion why is it important for trainees to work with a CTU, where possible, when undertaking research training relevant to clinical trials?

CTUs offer a wide range of trials that focus on patient-based clinical research typically with multidisciplinary expertise thereby offering applicants access to experiential learning opportunities enabling direct hands-on experience delivering all aspects of clinical trials. There are also wider opportunities available including understanding how proposals are developed from an initial idea through to sharing research ideas with colleagues and attending various meetings and committees which oversee the development of a CTU and its portfolio. This is essential career development for trialists capable of leading high quality multicentre randomised trials in the future. It also enables new researchers to start building strong relationships with CTUs at the start of their career.
What support does your CTU offer to people applying for fellowships and other research training awards?

- Access to a wide range of research experts, many of whom are international research leaders in their fields (e.g. clinical trials, statistics, data base management, programming, organisational research and health psychology).

- Access to the University of Aberdeen (UoA) research resource, including physical facilities in the HSRU (Health Services Research Unit; the administrative home of CHaRT), electronic facilities such as online resources and access to journals, and seminars and training events in CHaRT/HSRU and wider Institute of Applied Health Sciences.

- Support for data management and administrative aspects of the research project.

- Expertise in all key aspects of study management.

What models of support does your CTU provide to those undertaking a fellowship or other research training award?

Fellows can benefit from established and experienced mentoring and support structures within CHaRT and the UoA to enable them to thrive as newly independent investigators. HSRU is home to a leading group of post-doctoral fellows, RCUK fellows, a Health Foundation Improvement fellow and NHS Research (NRS) Scotland clinician fellows.

Fellows have access to the full range of development activities including monthly journal clubs, local training and lunchtime research group meetings. The UoA Researcher Development Unit (http://www.abdn.ac.uk/develop/) also provide a range of training courses.
Are there any other ways that your CTU supports individuals looking to further their career as a clinical trialist?

Advice & support with applications (grant & fellowship).

In your opinion why is it important for trainees to work with a CTU, where possible, when undertaking research training relevant to clinical trials?

A CTU provides an environment that is multi-disciplinary and multi-methods by design and the team addresses real-world health concerns with research expertise and excellence that comprises a range of complementary approaches. The environment is supportive in developing early career researchers, offering structured mentoring and encouragement to advance ideas.
Case Study:

Southampton Clinical Trials Unit

Jane Robertson
Head of Operations

What support does your CTU offer to people applying for fellowships and other research training awards?

Discussion around the application. Checking the application. Practice interview. Support in finding matching funding if required.

What models of support does your CTU provide to those undertaking a fellowship or other research training award?

Mentoring, peer support, access to SOPs and in house training provided to all new trial management staff.

In your opinion why is it important for trainees to work with a CTU, where possible, when undertaking research training relevant to clinical trials?

Clinical trial units have a wealth of experience regarding application for and delivery of trials. This experience can prove invaluable for those trainees wishing to move to submitting their own application and first CI opportunity.


9. FINANCES

What are NHS Service Support Costs?

The Department of Health guidance ‘Attributing the costs of health and social care Research and Development (AcoRD)’ [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/351182/AcoRD_Guidance_for_publication_May_2012.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/351182/AcoRD_Guidance_for_publication_May_2012.pdf) defines NHS support costs as ‘the additional patient care costs associated with the research, which would end once the R&D study in question had stopped, even if the patient care involved continued to be provided’. For the purpose of attributing costs during a research study, an assumption is made that the care/treatment under review will become standard. For example, if during a clinical trial patients require additional tests to pick up any adverse effects to the new treatment which wouldn’t need to be continued if the treatment later became standard care in the NHS, the costs of these additional tests would be classed as service support costs.

What is classified as an Excess Treatment Cost?

AcoRD guidelines classify NHS treatment costs as ‘the patient care costs, which would continue to be incurred if the patient care service in question continued to be provided after the R&D study had stopped’. So continuing the example from the above the NHS treatment costs would be the costs of treating the patients in the clinical trial that would continue if the new treatment later became standard care in the NHS. Excess treatment costs arise when the new treatment being trialled is more expensive than standard care.

The difference between the treatment costs of the new intervention and standard care is classed as the excess treatment costs. Of course the new intervention may be cheaper than standard care in which case a saving in treatment costs to the NHS will be observed.

How do I cost a clinical trial for an NIHR Fellowship application?

All NIHR application forms are accompanied by extensive guidance notes which detail what costs can and cannot be included in a particular application. Again this is another area where expert advice must be sought.
10. ADDITIONAL SUPPORT

What support can the Research Design Service offer?

The Research Design Service (RDS) supports research teams to develop and submit high quality applied health and social care grant applications to NIHR and other national peer-reviewed funding programmes.

The RDS offers specialist advice on all aspects of an application including:

- designing a research study
- research methods (qualitative and quantitative)
- identifying suitable sources of funding
- involving patients and public in research design
- identifying potential academic, clinical and lay collaborators

Their advice is confidential and free of charge.

For more information visit:

www.rds.nihr.ac.uk

Who can I contact for specific information about how to fit a clinical trial into an award?

Please direct all queries tcc@nihr.ac.uk and a relevant member of the team will contact you.
ADDITIONAL GUIDANCE FOR APPLICANTS
INCLUDING A CLINICAL TRIAL, PILOT STUDY OR FEASIBILITY AS PART OF A PERSONAL AWARD APPLICATION.
Introduction

This additional guidance is supplementary to the guidance provided in the completing the online application form section of the relevant programme guidance notes and should be read in conjunction with this guidance. The guidance below is aligned with the guidance provided to applicants for other NIHR programme funding and is intended to help applicants to NIHR personal awards think though the scope of any clinical trial, pilot study or feasibility study that is to be included within a personal award application. The guidance is particularly relevant to applicants thinking of including a feasibility study as part of a personal award application and is intended to make applicants think through the next stage of their research upon completion of the fellowship or other personal award.

Feasibility and Pilot studies

The definitions of pilot and feasibility studies below have been agreed across NIHR research programmes and all NIHR research training schemes where project funding is included.

We expect that when pilot or feasibility studies are proposed by applicants as part of a research training award, the applicant is clear about the route the substantive study will take upon completion of the training award. This will include having an appreciation of which funding stream to apply to for the substantive study, and having a clear understanding as to the requirements of that funding stream in terms of what the preliminary study should have achieved. Further details of the various NIHR programmes and their requirements for applications for substantive trials can be found here:

http://www.nihr.ac.uk/funding/research_programmes.htm
Feasibility studies

Feasibility studies are pieces of research done before a main study in order to answer the question “Can this study be done?” They are used to estimate important parameters that are needed to design the main study. For instance:

- standard deviation of the outcome measure, which is needed in some cases to estimate sample size;
- willingness of participants to be randomised;
- willingness of clinicians to recruit participants;
- number of eligible patients; carers or other appropriate participants;
- characteristics of the proposed outcome measure and in some cases feasibility studies might involve designing a suitable outcome measure;
- follow-up rates, response rates to questionnaires, adherence/compliance rates, ICCs in cluster trials, etc.
- availability of data needed or the usefulness and limitations of a particular database; and
- time needed to collect and analyse data.

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. It should be noted that an underpowered ‘exploratory trial’ is not the same as a feasibility study and is unlikely to be funded as part of a research training award.
The very nature of feasibility studies means that they are relatively high risk. On the one hand the end result may be to confirm that a full trial is not feasible and on the other hand, even if shown to be feasible, another funder may not be interested in supporting a full trial (because perhaps either the clinical question is not sufficiently important or there are ongoing trials in the area already in the portfolio). Applicants need to consider the likelihood of other NIHR funding programmes or other funders being interested in supporting a full trial in the future when including a feasibility study in a research training award application. The feasibility study should also represent a high quality training vehicle for the applicant around clinical trials and research training more widely.

**Pilot studies**

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, including an assessment of the primary outcome. 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.

**Feasibility and pilot studies: which programme should I apply to?**

Before deciding on which programme to apply you should first consider whether you want to apply for a personal research training award or funding to undertake a specific piece of research. NIHR personal research training awards e.g. Fellowships are not project or programme grants and any trial or feasibility study included in a training award must fit within the scope of what the award is designed to achieve (i.e. does it represent a suitable training vehicle for the trainee?) If you are looking for funding to undertake a particular piece of research then funding from one of NIHR’s research programme may be a more appropriate route.

For more information about NIHR’s research programmes please visit:

http://www.nihr.ac.uk/funding/research_programmes.htm.
Feasibility studies within a NIHR Research Training Award

Clinical trials are expensive and the chances of successful completion are improved if it can be shown beforehand that key elements (such as the ability to recruit patients) are feasible before the main study starts. NIHR will therefore fund such feasibility studies which are investigations carried out before a main study in order to answer the question “Can this study be done?” The research plan for a feasibility study should therefore contain a brief outline of the proposed main study and a list of the ‘uncertain’ important parameters that are needed to design the main study, as described below.

The Research Plan section of the application form should include:

1. A brief outline of the intended main trial.

Some of these details will of course depend on the results of the proposed feasibility research but a key part of evaluating the value of a feasibility study is whether or not a full trial is likely to get funded. You should therefore briefly describe as far as you can what the main trial would look like. This might include (if they are known), whether it’s an individual patient randomised or cluster trial, the number of arms, the inclusion criteria, the nature of the intervention and of the comparator in the control group, the primary endpoint, and the possible range of clinical sites from which patients would be recruited.
2. A list of the parameters which the feasibility study intends to clarify or estimate. These may include:

- the number of eligible patients, carers or other appropriate participants;
- an exploration of different methods of identifying/recruiting patients;
- the willingness of clinicians to recruit and randomise participants;
- the willingness of participants to be randomised;
- the practicality of delivering the intervention(s) in the proposed setting(s);
- variation in use or delivery of the intervention in each setting;
- acceptability of the intervention to the users;
- standard deviation of the outcome measure, which is needed in some cases to estimate sample size;
- follow-up rates, response rates to questionnaires, adherence/compliance rates, ICCs in cluster trials, etc;
- availability of data needed or the usefulness and limitations of a particular database;
- the time needed to collect and analyse data;
- exploring the opportunities for PPI (patient and public involvement) in the research design and its subsequent conduct.

In effect the research plan should describe which parameters are to be estimated and how these will be investigated.

3. A feasibility study does not necessarily need to include the following:

- a randomised design: the design will be determined by how it is proposed to reduce the uncertainty in the parameters described above
- an evaluation of the outcome of interest: that is left to the main study
- a primary outcome: if a feasibility study involves carrying out a small randomised controlled trial it is for the purpose of evaluating/testing trial processes not the intervention
- the usual sort of power calculation: the sample size should be adequate to estimate the critical parameters (e.g. recruitment rate) to the necessary degree of precision.
Clinical trials training as part of an NIHR Research Training Award

Anyone proposing to include a clinical trial as part of a research training award needs to bear in mind the primary purpose of any award is to provide an excellent training experience for the trainee. This is achieved through conducting a relevant and high quality research project or programme complemented by formal training, placements, research visits, collaborations, supervision and/or mentorship. With this in mind it is important that applicants proposing to include a clinical trial think through the wider aspects of clinical trials training and the skills and experiences they need. The award as a whole must represent a high quality training vehicle for someone who wants to make a step change in their trajectory towards becoming a future health research leader competent in the design and conduct of clinical trials.

NIHR does not dictate what the training within a fellowship should be or how it is delivered as it should be bespoke to an individual’s needs and requirements. However it is very important that the trainee experiences all elements of clinical trials from idea to dissemination. It is particularly important for example to ensure training in patient and public involvement and health economics (where needed) is included early in the lifecycle of a training award to ensure these elements can be utilised right from the inception of the study.
Below is a list of key skills that applicants should consider when putting together an application focused around clinical trials. The list is intended to cover all aspects of clinical trials that future health research leaders competent in clinical trials should be knowledgeable in and it may not be necessary for a training award to encompass all these elements depending on the skills and experience the applicant already has.

- Evidence based medicine and critical appraisal of clinical trials
- Systematic reviews
- Basic statistics for clinical trials including power calculations
- Clinical trial design and protocol design
- Complex interventions and intervention development
- Randomisation
- Blinding
- Governance including; GCP, regulatory requirements, ethics.
- Recruitment
- Data collection, processing and management
- Data analysis
- Trial reporting, dissemination and impact
- Patient and public involvement
- Outcome measurement
- Health economics
- Priority setting and question development
- How to reduce bias and research wastage
- Funding for pilot and feasibility work
- Multidisciplinary working encompassing leadership, networking, and collaborating
- Ideas generation
In order to experience all the elements of a clinical trial as described above it may also be beneficial to gain exposure to the following as part of any research training award:

– Trial development groups
– Trial management groups
– Data monitoring and ethics committees
– Trial steering groups
– Dissemination meetings

Another important consideration when thinking through a research training application involving a clinical trial, particularly at PhD level, is whether the proposal will meet the requirements of a PhD to be ‘new and original research’ given that an RCT is highly multidisciplinary teamwork. A suitable project at PhD level for someone wanting to develop their career in clinical trials may not involve actually undertaking a clinical trial or feasibility study. It may be more appropriate and beneficial to consider projects based more around the methodology of clinical trials, for example a PhD focussed on a particular theme across several clinical trials such as recruitment, retention, qualitative studies in advance of a trial, obtaining consent, data analysis, or novel trial designs.

It is also important to link with and get input from other parts of NIHR when putting together an application focussed on clinical trials. For example early discussions with the Clinical Research Network (www.crn.nihr.ac.uk), Research Design Service (www.rds.nihr.ac.uk) and relevant Clinical Trials Unit (CTU) (http://www.ukcrc-ctu.org.uk) are strongly advised before starting an application. To order to help you identify a suitable CTU that is potentially willing to collaborate with you and support your training and development, the UKCRC Registered Clinical Trials Unit Network has a resource finder where you can search for a CTU based on various criteria. You are able to search for CTUs that are interested in supporting fellowships and other research training award applications and also search based on the disease area, study type and methodological expertise of the CTU. The resource finder is available to use at www.ukcrc-ctu.org.uk/search/custom.asp?id=468
Points to consider when evaluating established interventions

Many types of intervention such as cognitive behavioural therapy (CBT), exercise and outreach have been shown to be widely effective. Even so NIHR programmes, frequently receive applications for further evaluations of the effectiveness of such approaches or variants of them in different populations and for different indications. In judging such applications, three common questions arise:

Is a new trial in a different target population justified?

A common type of proposal is to evaluate (through a trial or trial feasibility study) the effectiveness of an intervention for a condition for which it has already been tested, but in a new population – for example, an exercise intervention in young people, old people or ethnic minorities. Another common application is for funding to evaluate the intervention in a familiar population that has a physical condition not previously included in previous research – prostate cancer, multiple sclerosis, frequent attendance in primary care and so on. These may be important research questions but a panel will reasonably ask if results suggesting effectiveness in previous research can be extrapolated to the new population or condition so that further research is not needed. After all, the popularity of some interventions such as CBT and exercise encouragement resides in being flexible therapies defined by some general principles, the detailed content of the intervention often being tailored to individual need during therapy.

When submitting applications for evaluating an established intervention in a new target population or condition it is therefore important to identify why and how the new target is different from others that have already been researched. An application justified simply by stating that the intervention has never been tested in the proposed target population is unlikely to be successful if that is the only rationale. A case needs to be made that the new target population or condition has important differences that make extrapolation from previous work inadvisable - for example that the new population has been shown to have a different response to other therapies in other studies, or the new physical condition poses challenges that have not been addressed in previous trials. In short, it is not the absence of evidence that best justifies new studies but the distinctiveness of the target population.
Is a trial of a new variant of an established intervention justified?

The second type of study that is frequently received by the programme is testing of another therapy based upon modifying the form or content of an established one. There are two issues for panels to consider here.

First, proposals may not change the content of therapy but propose different formats for delivery – for example using computerised CBT, smartphone apps or therapists from different disciplines to deliver the intervention. In this situation it is unlikely that the new variant would have considerably greater effectiveness than the conventional therapy and the rationale is usually that cost-effectiveness can be increased by the new format. In many instances further research may not be justified: it might seem a reasonable inference that if, say, chronic obstructive pulmonary disease (COPD) nurses can deliver CBT effectively then cancer nurses or health visitors can too. But if a trial is proposed, the required non-inferiority design will need a large and therefore expensive study and applicants need to bear in mind that the cost of any trial might be judged as outweighing the potential incremental benefit to be achieved. Alternatively, new formats need to be justified by evidence that they are likely to increase coverage or retention in therapy and will therefore be more effective at a population level.

Second, a new variant is sometimes proposed because it is argued that an existing generic intervention does not adequately treat the population or the condition under consideration. Examples might include modification to respond to specific symptoms not otherwise addressed or to specific features of the target population. Since, as noted above, many of these interventions are characterised by their flexibility, a panel will reasonably ask if the proposed variant is really new or simply codifies what a competent therapist would do anyway. Applications for variants of established interventions therefore need to make a strong case either that the new therapy is likely to be considerably more effective (or cheaper) than the existing one if the latter is delivered according to accepted standards.
What facet of the intervention is being evaluated?

The exact active ingredient in many interventions is not well understood. For example, there are two other components of the response to talking therapies from which the CBT effect needs to be differentiated. One is the non-specific effect of concerned attention, represented for example in the frequency and number of sessions. The other is generic therapeutic effects - the therapist’s skills and experience, the strength of the therapeutic alliance and so on. CBT is a limited and expensive resource in the NHS and applications will need to demonstrate that any effect demonstrated by the proposed intervention can reasonably be attributed to CBT and not to something that could be delivered more cheaply and just as effectively by other means.

Useful References and Resources


The MRC provide a course entitled; ‘How to be a good Chief Investigator,’ details of which can be found here: http://methodologyhubs.mrc.ac.uk/workshops

NIHR video; ‘The role of Clinical Trials Units in developing an NIHR funding application’: https://www.youtube.com/watch?v=QvGaGEHgwXg&feature=youtu.be.

11. SUMMARY OF USEFUL LINKS

- Completed systematic reviews
  www.cochranelibrary.com
  www.crd.york.ac.uk/CRDWeb

- Ongoing systematic reviews
  www.crd.york.ac.uk/PROSPERO

- Ongoing clinical trials
  www.ukctg.nihr.ac.uk/default.aspx
  www.isrctn.com
  https://clinicaltrials.gov
  http://apps.who.int/trialsearch

- Feasibility and pilot studies
  www.nets.nihr.ac.uk/glossary?result_1655_result_page=F
  www.nihr.ac.uk/CCF/RfPB/FAQs/Feasibility_and_pilot_studies.pdf

- Trial risk levels
  www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Submittinganotificationforatrial/index.htm

- Regulatory body approval
  www.hra.nhs.uk/research-community/applying-for-approvals
  www.mhra.gov.uk/Howweregulate/index.htm

- Trial governance
  www.crn.nihr.ac.uk/learning-development/good-clinical-practice/
  www.hra.nhs.uk/research-community/during-your-research-project/

- Publishing the protocol of a clinical trial
  www.ct-toolkit.ac.uk/routemap
- Types of trial
  www.nihr.ac.uk/CCF/RfPB/FAQs/Feasibility_and_pilot_studies.pdf
- Study design
  www.ct-toolkit.ac.uk/routemap/trial-planning-and-design
- Minimising bias
  http://handbook.cochrane.org/
- Clinical trial proposals
- Teams and management
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917433/
- Patient and public involvement (PPI)
- Clinical Trials Units (CTUs)
  www.ukcrc-ctu.org.uk/
  www.nets.nihr.ac.uk/programmes/ctu
- NHS support costs
For more information on pursuing a clinical academic career, or supporting a colleague to do so, contact:

NIHR Trainees Coordinating Centre
Leeds Innovation Centre
103 Clarendon Road
Leeds
LS2 9DF
Tel: 0113 346 6260
TCC@nihr.ac.uk