Cardiff University
Prifysgol Caerdydd

Centre for Trials Research
Canolfan Ymchwil Treialon

Working with the Centre for Trials Research, Cardiff University

A collaborator's guide

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan Lywodraeth Cymru
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CANCER RESEARCH UK

www.cardiff.ac.uk/centre-for-trials-research

“Working with the Centre for Trials Research has enabled me to deliver world-leading trials, including being published in both the Lancet and the New England Journal of Medicine.

A team of experts in a Clinical Trials Unit facilitates running trials to a very high standard and means every aspect of a study will be robustly managed, compliant and follows best practice.

To have the diverse group of experts needed to deliver high-quality trials all in the one place means studies are much more likely to be done efficiently, timely, and to the highest international standards.”

Professor Chris Butler,
University of Oxford

This guide

This guide is for investigators considering or currently collaborating with the Centre for Trials Research. It describes who we are, how we are funded, how we take on new work, the main responsibilities assumed by both Centre staff and Chief Investigators, the teams working within the Centre and key contacts.

About us

The Centre for Trials Research, Cardiff University is a UKCRC[1] fully registered trials unit. Registration provides collaborating investigators assurance that the Centre has the capability to centrally coordinate national and international multi-centre clinical trials. This means that we are able to design, develop, recruit to, data manage, analyse and disseminate a portfolio of trials. We have demonstrably robust systems to conduct and deliver clinical trials to the highest quality standards.

Centre funding

The Centre for Trials Research is core funded by Welsh Government through Health and Care Research Wales, and by Cancer Research UK. Cardiff University funds some core academic and professional service staff. All Centre projects are supported through externally derived grant funding.

Where we are based and work

The Centre for Trials Research is located in Neuadd Meirionnydd on Cardiff University's Heath Park Campus. Working in the College of Biomedical and Life Sciences we actively collaborate with all Schools of the College, as well as other Colleges and Schools in Cardiff University. We are part of the health and social care research infrastructure in Wales and actively work with all health boards and higher education institutions in Wales and beyond. Our open door policy means that any researcher, health or social care practitioner is welcome to approach us about collaborating or gaining advice.

Our research

The Centre runs a wide range of studies including clinical trials of investigational medicinal products (CTIMPs), trials of health and social care interventions, quantitative and qualitative observational studies and systematic reviews. The approach we take will be driven by the research question. We have four divisions, each led by a Director and Deputy Director, reflecting our major strategic areas of (i) Cancer, (ii) Infections, Inflammation and Immunity, (iii) Mind, Brain and Neuroscience and (iv) Population Health. Through our Research Design and Conduct Service (RDCS) we also provide advice to health and social care professionals in Wales interested in developing their research ideas to the point of a funding application.

Our staff

Our research and professional services staff provide capacity to run to high quality a wide range of studies. Our teams comprise trial managers, statisticians, data managers, qualitative methodologists and professionals in quality assurance and regulatory affairs, information technology, information systems and database development, study and operations administration, and communications (see Appendix 1). Centre staff are trained in our extensive quality management system meaning that they are suitably qualified to run regulatory compliant studies to high quality.

[1] The UK Clinical Research Collaboration (UKCRC) was established in 2004 with the aim of re-engineering the clinical research environment in the UK, to benefit the public and patients by improving national health and increasing national wealth. The Partnership brings together the major stakeholders that influence clinical research in the UK. It includes the main UK research funding bodies; academia; the NHS; regulatory bodies; the bioscience, healthcare and pharmaceutical industries; and patients.

Taking on new work

We encourage good ideas from all potential collaborators. It is often most useful to have early conversations so that our team can help collaborators to work up their initial ideas and research questions. To take on any new work a brief study outline needs to be reviewed by a monthly adoption committee. This will involve considering the study's strategic fit, design quality, the potential beneficial impact for patients and the public, current capacity and timescale for supporting a funding submission, resources being identified for the study and appropriateness of plans for public involvement. Presentation to the committee will be sponsored by a nominated lead from within the Centre who would normally be responsible for drafting the application for adoption in discussion with the person who approached us with the idea. Most requests reviewed will lead to studies being adopted, sometimes with some suggested modifications or a request for clarification. Studies not initially adopted may still be considered at a later date, usually after some further development of the study proposal.

Study funding

Staff to work on Centre studies will usually need to be costed into funding applications. This will include required time for all investigators, research and professional services staff. Requirements will vary by funder and we can advise on this. Centre teams operate costing frameworks to help guide discussions on study resources. In some cases existing Centre staff can be costed into funding applications and their time bought out to work on funded studies, as well as new staff being appointed to the study.

Study leads

For all adopted studies, a Centre study lead will be identified. They will act as the principal point of contact between the study Chief Investigator (CI) and the Centre. This will usually be one of the Centre academic or research staff. Good communication between members of the study team and the Chief Investigator is essential and the study lead is there to facilitate that. Periodic review of study progress through discussion between study lead and CI is encouraged.

Models of working

At study adoption, the preferred way of organising the work will be discussed and agreed with the Chief Investigator. This determines the responsibilities assumed by the Centre and those that are retained by the Chief Investigator (and others as appropriate). There are two main models of working we operate. The first model involves the Centre fully coordinating study conduct. In practice this means that many key responsibilities for running the study are delegated to the Centre. The second model involves the Centre taking responsibility for a sub-set of study activities. An example of this may be where all data management, statistical analysis and reporting is delegated to the Centre but all other aspects of the study are the responsibility of another organisation. Whichever model is used and whoever assumes responsibility, all parties will need to agree that arrangements are adequate for the study to be delivered to a high standard.

Identifying and agreeing study responsibilities

Key to successful collaboration is the early identification and allocation of key study responsibilities. We have listed in appendix 2 some of the main responsibilities that are likely to be relevant to most studies. This is just a guide and should serve as the basis for discussion with the team from the Centre when developing a funding application.

Role of the Chief Investigator

The CI takes responsibility for the conduct of the research and would normally be a researcher who is professionally based in the UK and therefore able to effectively oversee the research. They must be available to communicate with the relevant research ethics committee and other regulatory bodies during set-up and conduct of the research in collaboration with the Centre. The CI is responsible to the funder to deliver the study in accordance with the terms and conditions of the award. They are responsible for delivering the primary publication of the work in collaboration with the Centre and collaborating investigators.

Public involvement and engagement

We are committed to high quality and meaningful public involvement and engagement in all our studies. How this will operate may vary between studies and we can advise on what is most appropriate for each study. In most cases this will also involve requesting resource to support public involvement in funding applications consistent with national guidance.

Values based relationships

As a Centre we are committed to a set of values that recognise the importance of respect and support for everyone, both internal and external. As part of this we have developed a clear set of guiding principles for how we work and we encourage these to be recognised by our collaborators as well as all of our staff.

Key contacts:

Centre Director: Professor Kerenza Hood

Centre Manager: Mr Damian McAuliffe

Cancer
Director: Professor Richard Adams

Infections, Inflammation, Immunity
Director: Professor Kerenza Hood
Deputy Director: Dr David Gillespie

Mind, Brain, Neuroscience
Director: Professor Monica Busse
Deputy Director: Dr Rachel McNamara

Population Health
Director: Professor Michael Robling
Deputy Director: Dr James White

Research Design and Conduct Service (SE Wales)
Director: Dr Sue Channon
Deputy Director: Dr Philip Pallmann

“Working with the Centre for Trials Research has been invaluable in securing grant funding and running a multi-centre randomised controlled trial. The Centre provides the Chief Investigator with support from day to day dealing with the funder and the recruiting sites, to regulatory approvals, finance and budgeting, sponsorship, industry liaison, and all the other bureaucracy around clinical trials.

The trial manager is the first point of contact for these issues, and deals with them on a day to day basis, thus allowing the Chief Investigator to focus on the research. Any new Chief Investigator or Principal Investigator wants to know that their research is of the highest quality, and they don’t have to be bogged down with the administrative aspects of running a randomised controlled trial (RCT).

Working with the Centre gives me absolute confidence that the RCT is being conducted to the highest standards, and that the final results will be used to inform clinical practice, safe in the knowledge that current best practice in trial management has been followed throughout.”

Professor Enitan Carrol,
University of Liverpool

Appendix 1

A quick guide to teams in the Centre for Trials Research

Trial managers

The trial management team are responsible for overall project management, including monitoring of recruitment and retention rates, project-specific budgets and timelines. Trial managers ensure studies are conducted according to appropriate research governance and regulatory requirements, including development of the study protocol and coordination of ethics and research governance submissions.

Statisticians

The statistics team provide expert design advice for grant submission. If successful, all statistical aspects of the study are designed, tested and monitored while analyses are carried out following detailed analysis plans to ensure high quality results. Interpretation and report writing are then carried out together with the study team.

Data managers

The data management team are responsible for ensuring that the data in Centre for Trials Research studies is of the highest quality. Through the processes and procedures that the team put in place our investigators are able to have confidence that the data collected will be able to answer their research questions.

Qualitative researchers

The qualitative research team contribute methods expertise to a wide range of studies. This will include observational studies where the dominant approach may be qualitative through to large scale multicentre trials. Applying qualitative methods may be essential at different stages of the research lifecycle, for example, for initially exploring the needs of patients and the public, to understanding their experiences in interventional studies through to supporting dissemination.

Information systems and database developers

The information systems and database development team are responsible for building and maintaining the systems which support the Centre's research. This covers a wide range of databases and online systems which work across PCs, tablets and smart phones. The team are a mixture of experienced managers and programmers, and computer science graduates.

Study administrators

The administration group provide an administrative service to the Centre, engaging with and completing a range of routine tasks to meet operational and study service requirements.

The team provide support and guidance on administration tasks to ensure the Centre and our studies are supported with key administrative duties undertaken in accordance with regulatory requirements. The team have a diverse range of experience in management and administration.

Quality assurance and regulatory affairs

The quality assurance and regulatory affairs (QA and RA) team have wide-ranging experience in clinical trials of investigational medicinal products, interventional trials and observational studies. The QA and RA team are responsible for ensuring adherence of Centre studies with the relevant regulatory requirements and the central management and reporting of safety.

Changing the nature of trials

Staff in the Centre have expertise in methodological areas strategically important to changing the nature of trials. This includes utilising novel trial designs, making trials more efficient in both design and conduct and maximising the secondary use of existing data. The latter is supported by our routine data strategy group which looks at both design and practical solutions for using data potentially available from a range of providers.

Appendix 2

Typical responsibilities of Chief Investigators and Centre for Trials Research

Outlined below are responsibilities usually assumed by Centre staff or by Chief Investigators in studies fully coordinated by the Centre. The list reflects that many studies are trials, including clinical trials but can be adapted easily to suit specific study requirements and other study designs.

Milestones in a typical study lifecycle

1 Grant development and submission

2 Protocol and study development

- Protocol
- Sponsorship application
- Health Research Authority and regulatory approval
- Case report form / Questionnaire design and other data collection tools
- Safety / Pharmacovigilance
- Risk assessment

3 During the study

- Protocol
- Statistical analysis plan
- Monitoring and recruitment
- Reports
- Safety / Pharmacovigilance

4 End of study

- End of study reports
- Publication of final study manuscript

5 Throughout the course of the study

- Communication
- Trial Management Group, Data Monitoring Committee and Trial Steering Committee Meetings
- Inspections
- Data storage

1 Grant development and submission

The Centre will:

- Ensure the collaboration process is efficiently managed and allow sufficient time to support the CI in the development of the grant funding application.
- Provide appropriate support to enable the CI to submit a complete and competitive grant application including but not limited to, study design, statistical design, project planning, research costs, contacting co-investigators and collaborators and review of the final application.
- Work with local Clinical Research Network (CRN) and NHS partner to determine the research, service support and excess treatment costs associated with the project.

The CI will:

- Work with the Centre to develop the grant application at all stages (outline/full/single stage) and allow sufficient time for collaborators to make a meaningful academic contribution.
- Provide advice and guidance on the costing model for the study.
- Answer costing queries relating to the patient pathway to ensure proper cost attribution.
- Include senior Centre staff as co-applicants as appropriate.
- Discuss with the Centre planned substantial changes in the study design / conduct prior to grant submission.
- Provide a final copy of the grant submission to the Centre. Notify the Centre of the funding decision as soon as possible.

2 Protocol and study development

Protocol

The Centre will:

- Provide the CI with an initial draft of the trial protocol based on the Centre's protocol template.
- Co-ordinate the multidisciplinary input from a team of experts in the required fields from both within and external to the Centre.
- Ensure the Centre and Sponsor team contribute the relevant sections of the protocol to support the CI in the writing of the protocol (e.g. statistics, pharmacovigilance, pharmacy).
- Manage the protocol review process.

The CI will:

- Work on the initial draft of the study protocol using the Centre protocol template providing clinical input and expertise.
- Support the review process in order to finalise the study protocol.
- Ensure the protocol has undergone scientific and statistical review.

Sponsorship application

The Centre will:

- Ensure the correct sponsorship application process is followed based on local policies.

The CI will:

- Review and confirm the sponsorship application is complete and accurate prior to submission.
- Provide input into the sponsorship application process as required.
- Ensure all correspondence with sponsor is provided to the Centre.

Health Research Authority (HRA) and regulatory approval

The Centre will:

- Create and control the Integrated Research Approval System (IRAS) application for the study.
- Support the CI in the completion of the required regulatory documentation including Patient Information Sheet (PIS) and Informed Consent Form (ICF).

The CI will:

- Support Centre staff in the completion of all necessary regulatory submissions and ensure these are made within the expected timelines of the grant award.
- The CI must review and approve the PIS and ICF prior to submission for ethical approval.

Case report form (CRF) / Questionnaire design and other data collection tools

The Centre will:

- Manage the drafting process in parallel with the protocol drafting.
- Create a final version of the CRF / questionnaire using the Centre's approved template / process and update this as required during the course of the trial.

- Ensure the completion of a data management plan in line with Centre standard operating procedures (SOPs)
- Facilitate statistical review of data collection forms.
- The Centre database development team and study team will:
  - Create a validated study database.
  - Create all required IT support systems ensuring they are appropriately validated.

The CI will:

- Provide input, review and approve the CRFs / questionnaires prior to the study opening, ensuring that all data are captured as detailed in the protocol to answer the study endpoints.
- Provide clinical input during the CRF / questionnaire drafting process and any amendments required throughout the study.

Safety/Pharmacovigilance (PV)

The Centre will:

- Liaise with the sponsor, CI and pharmacy with respect to the identification and approval of appropriate Reference Safety Information (RSI) for all Investigational Medicinal Products (IMPs) for the study (CTIMPs only).
- Liaise with sponsor and CI regarding safety reporting requirements for example, timeframes, excluded events and coding systems.

The CI will:

- Help with the identification of appropriate RSI for all IMPs in preparation for submission to the Medicines and Healthcare products Regulatory Agency (MHRA) (CTIMPs only).
- Ensure the risks and side effects listed in the patient information sheet are consistent with the RSI for all IMP(s) (CTIMPs only).
- Advise on the safety inclusions / exclusions to reporting.
- Identify sufficient medically qualified individuals to review and assess trial safety events.

Risk assessment

The Centre and the CI are jointly responsible for the study risk assessment (RA). The RA requires a co-ordinated multidisciplinary approach across the study team.

The Centre will:

- Generate a RA using the Centre's template.
- Co-ordinate the input from a team of experts from both within and external to the Centre.

The CI will:

- Provide clinical input into the risk assessment.
- Conduct final review and sign off the RA.

❸ During the study

Protocol

The Centre will:

- Prepare all protocol amendment documentation in consultation with the study team and the sponsor.
- Submit amendments to all the required bodies in a timely manner.

The CI will:

- Ensure all protocol amendments are reviewed and agreed.

Statistical analysis plan

The Centre statistician will:

- Write the Statistical Analysis Plan (SAP) and develop, test, validate and monitor the randomisation.

The CI will:

- Review and approve the SAP.

Monitoring and recruitment

The Trial Management Group (TMG), which will include the CI, will:

- Actively oversee recruitment to the study and where necessary agree / implement strategy where recruitment is not in accordance with initial plan.

Reports

The Centre will:

- Initiate and prepare report(s) for submission to applicable bodies as laid out in the terms and conditions of approval / funding in collaboration with the study team.

The CI will:

- Contribute to reports to applicable bodies / funder.
- Author sections of reports as indicated by the Centre.
- Provide timely review, approval and signature on all reports.

Safety / Pharmacovigilance

The Centre will:

- Send reports / e-mails of all new Serious Adverse Events (SAEs) to the CI for medical oversight.
- Communicate information regarding potential Suspected Unexpected Serious Adverse Reactions (SUSARs) / safety events to the CI.
- Provide current approved RSI for IMPs to the CI for advice on the clinical management of study participants and consideration of expectedness.
- Ensure updates to source RSI are provided to the CI for review and assessment.
- Prepare Development Safety Update Reports (DSURs).
- Ensure the Centre is in receipt of all required safety alerts from both the MHRA and marketing authorisation holders where appropriate.

The CI will:

- With input from the study statistician and any oversight committees review all new SAEs for the study in order to ensure CI oversight of safety reporting and if any unexpected, untoward safety issues or unanticipated patterns of SAE reporting are identified, the CI will alert the Centre immediately.
- Review SAEs for causality and expectedness.
- Answer safety related queries and identify SUSARs.
- Review safety alerts.
- Review literature to ensure the team are aware of the relevant clinical developments and safety information.
- Give a clinical opinion on any changes to the trial risk benefit assessment and the clinical management of patients following the update of RSI and completion of the DSUR for IMPs and advise of any changes required to the PIS, management of the study and protocol.
- Complete RSI review on receipt of update.

4 End of study

End of study reports

The writing, approval and distribution of the end of study report is a team responsibility and although the Centre can facilitate the activity it needs input from all parties.

The Centre will:

- Co-ordinate the writing of end of study report(s) for submission to applicable bodies liaising with all collaborators and investigators as appropriate.
- Prepare and submit end of study notification to applicable bodies.
- Upload results to the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT).

The CI will:

- Author sections of the end of study report as indicated by the Centre.
- Edit, review, approve, and sign off end of study reports.

Publication of final study manuscript

The Centre will:

- Contribute in manuscript preparation as directed by the CI.
- Help to identify the target journal(s) for publication.
- Provide a final statistical report and statistical input into the manuscript in line with the SAP.

It is generally expected that Centre researchers will be co-authors on study outputs.

The CI will:

- Initiate and lead on the preparation of the final study manuscript process.
- Identify the target journal(s) for publication.
- Review and approve the final statistical report.
- Identify who will be involved in the writing up of the final study manuscript.
- Produce the final study manuscript (ready for submission).

5 Throughout the course of the study

Communication

The CI will:

- Be responsive to communication requests from the study team in a timely manner and will be respectful of the expertise each discipline contributes.

Trial Management Group (TMG), Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) Meetings

The Centre will:

- Organise and administer TMG, DMC and TSC meetings.
- Advise on suitable statisticians to sit on oversight committees.

The CI will:

- Chair the TMG meeting and lead the discussions.
- Contribute to DMC and TSC meetings.
- Advise on suitable membership.

Inspections

The Centre will:

- If the study is selected prepare the Trial Management File (TMF) ready for inspection.

The CI will:

- Attend for interview as required.

Data storage

The Centre will:

- Ensure data are stored and backed-up in line with the regulations.

Appendix 3

Typical role responsibilities of CTR study team staff

Trial manager

- Study development
- Coordinate protocol writing and revision
- IRAS application (MHRA and Research Ethics Committee (REC))
- Produce all study related documentation (e.g. site logs, patient information sheets)
- Manage study budget and payment to sites
- Main contact with sponsor representative
- Site feasibility assessment
- Promotion of the study including newsletters
- Support the reporting of protocol deviations
- Writing and processing of amendments
- Annual report to ethics
- Facilitate the contracts process
- Support the data management process
- Review and contribute to the writing of the study manuscript
- Presentation of study and results as required
- Main contact within the Centre for study sites
- Liaising with pharma partner during study set-up for IMP development – including creating drug order forms, user acceptance testing (UAT) for Interactive Web Response System (IWRS) in blinded studies, label development
- Preparation of Good Clinical Practice (GCP) Approved IMP label text for MHRA submission
- Preparation of IMP manuals for site and sponsor and associated pharmacy accountability / destruction logs and forms
- Conducting pharmacy training via pharmacy site initiation calls before study opening
- Completion of pharmacy site activation form
- Co-ordination of resolution of temperature deviations occurring during storage of IMP at site
- Preparing 'Notification of New Batch Release' documentation for any new batches of IMP
- IMP 'green light'
- Co-ordination of IMP orders from sites
- Oversight of IMP stock at site via IWRS
- Expiry date tracking of IMP at sites and at IMP depots (including highlighting to pharma partner when new campaigns required)
- Informs sites via Trial manager of last dispensing dates of IMP
- Co-ordination / escalation of site queries regarding IMP
- Gives permission to destroy any unused / expired IMP at sites
- IMP manual and accountability log updates where relevant for amendments
- Reconciliation of IMP at sites at study close out
- Oversee consumables budgets

Senior trial manager

- Study design and development
- Project oversight
- Review and approve the study protocol
- Review and approve the study CRF
- Review and approve the electronic case report form (eCRF)
- TMG member
- Troubleshoot problems
- Oversee budgetary issues especially relating to staff

Data manager

- Data management, including drafting study metadata, drafting data management plan, review of data, sending data queries, chasing sites for outstanding data and data cleaning
- Support the reporting of protocol deviations
- Processing of amendments and documentation to sites
- Review and contribute to the writing of the study manuscript
- Entering the randomisation test cases to test the randomisation algorithm
- Design the study CRFs
- Oversee the development of the eCRF

Pharmacovigilance

- Review and approve the study protocol
- Write the PV plan for the study
- Data management of SAE data – data entry, sending data queries and chasing sites for outstanding data
- Support the PV Manager with annual reports to Ethics and MHRA
- TMG member

Study administrator

- Support the TM with any administrative tasks relating to the study
- Site set-up and initiation coordination
- Manage site access to eCRF
- TMG member and minute taking
- Filing of paperwork, chasing outstanding data
- Site closure and archiving support

Database developer

- Produce test cases for the testing of the randomisation algorithm
- Development of the eCRF
- Writing reports from the database
- Oversee and deliver database amendments during life time of the trial
- Sample tracking database development
- Allow the central laboratories to track sample return

Statistician

- Study design and development (senior)
- Review and approve the study protocol (senior)
- Write and test the randomisation algorithm
- Write the SAP
- Review and approve the study CRFs
- Review and approve the eCRF
- Review and approve the study metadata
- Ongoing review of study data
- Ongoing analysis of study data
- TMG, DMC and TSC member
- Provide interpretation and explanation of the statistical analysis to the study team
- Produce final study report
- Review and contribute to the writing of the study manuscript
- Presentation of study and results as required

Contact us

The Centre for Trials Research is willing to consider any idea for a well-designed study or trial, even those outside its current areas of research. For more information about collaborating with our research team or to keep up to date with news and events:

Email: **ctr@cardiff.ac.uk**

Tel: **029 2068 7620**

Twitter: **@CTRCardiffUni**

Blog: **blogs.cardiff.ac.uk/centre-for-trials-research**

Website: **www.cardiff.ac.uk/centre-for-trials-research**