Standard Operating Procedure CCTU/SOP070

Set-up procedures for CCTU-led non-CTIMP clinical research trials

1. Scope

This SOP applies to Cambridge Sponsored non-CTIMP clinical research trials conducted in collaboration with the CCTU.

This SOP does not cover commercial research

2. Purpose

The purpose of this SOP is to ensure that non-CTIMP clinical research trials are set up and conducted in accordance with CCTU procedures and follow Sponsor Research Governance, GCP, UK policy framework for health and social care research.

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC OR Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Externally Sponsored	Sponsored by any other Trust, University or Commercial Organisation outside the CUH, CPFT or UoC remit.
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial
CTIMP	Clinical Trials of Investigational Medicinal Product
Non-CTIMP clinical research trial	This can be any trial that does not involve an IMP and does not, therefore, fall in the scope of the EU regulations for medicinal products. Non-CTIMPs can include observational trials, interventional trials, randomised controlled trials, device trials. Non-CTIMPs can involve drugs but not under the definition of IMP.
Trial Team	Includes the Chief Investigator (CI) and other members of staff at the coordinating centre delegated trial activities by CI and Sponsor, e.g. Clinical Trials Coordinator, Data Manager, Trial

	statistician, Database Programmer, Research Nurse etc.
IRAS	A UK-wide system used to prepare applications to REC, HRA, ARSAC, MHRA, the NIHR CRN portfolio (this list is not exhaustive).

3.2. Abbreviations

Abbreviation	Meaning
ARSAC	Administration of Radioactive Substances Advisory Committee
CA	Competent Authority
CCTU	Cambridge Clinical Trials Units
CI	Chief Investigator
CRF	Case Report Form
pCRF	Paper Case Report Form
eCRF	Electronic Case Report Form
CRL	Collaborative Research Letter
CRN	Clinical Research Network
CTC	Clinical Trials Coordinator
CUH	Cambridge University Hospitals NHS Foundation Trust
DM	Data Manager
GCP	Good Clinical Practise
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trials Number
ISF	Investigator Site File
LIP	Local Information Pack
NIHR	National Institute for Health Research
MHRA	Medicines and Healthcare Products Regulatory Agency
PAF	Portfolio Adoption Form
PCA	Pre-Clinical Assessment
PI	Principal Investigator
PIS	Participant Information Sheet
RAC	Research Advisory Committee
REC	Research Ethics Committee
R&D	Research and Development
SoA	Statement of Activities
SoECAT	Schedule of Events Cost Attribution Template
TMF	Trial Master File
UoC	University of Cambridge

4. Undertaken by

CCTU staff and trial team members working on research trials in collaboration with CCTU. This may include coordinators, research nurses, and other delegated members of the trial team.

5. Items Required

CCTU/SOP054	CCTU Funding and Collaboration Process
CCTU/TPL001	Protocol Template
R&D/TPL005	Protocol Template NON CTIMPs only
R&D/POL005	Review and Set-up Process for Confirming Capacity and Capability
R&D/SOP005	Management of Contracts for Research Projects
CCTU/GD012	Initial HRA/REC Submission Guidance
CCTU/SOP039	Setting up and Opening a Participating Site for Trust Sponsored Trials
CCTU/TPL065	Registration of Interest/Feasibility template
CCTU/TPL009	Data Management Plan
CCTU/SOP015	TMF & Site File Essential Document Management
CCTU/TPL032	Trial Master File Index
CCTU/GD026	Trial/Study Management Groups and Committees
CCTU/SOP024	Initiation Meeting for CTIMPs
CCTU/GD049	CCTU Led Non CTIMP Risk Mitigation Guidance
CCTU/FRM112	CCTU Led Non CTIMP Risk Assessment Form
CCTU/TPL082	CCTU Led Non CTIMP Monitoring Plan
CCTU/SOP071	Selection of Laboratories for Analysis of Research Samples
CCTU/SOP044	Research Sample Management
CCTU/SOP045	Use of Vendors
CCTU/SOP064	Setting up International Sites
R&D/POL003	Trust Sponsored International Trials
CCTU/TPL048	Variable List
CCTU/SOP013	Paper Case Report Form Design
CCTU/GD033	Using CRF Generator to Design Trial Data Capture
CCTU/SOP049	Data Management Tools and Procedures
CCTU/SOP055	Using the CRF Generator to Create Tools to Capture Clinical Trial Data
CCTU/SOP036	Open Label Randomisation
CCTU/SOP046	Blinded Randomisation
CCTU/SOP053	Paper Based Randomisation
CCTU/SOP005	Test of Out of Hours Medical Cover Arrangements

6. Summary of Significant Changes

New

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Meeting with CI to discuss the start of the collaboration

- Following confirmation of funding for the proposed trial and signing of the CRL (refer to CCTU/SOP054 CCTU Funding and Collaboration Process) senior

staff from the relevant CCTU theme will meet with the CI to discuss details of the trial and agree timelines

- SOPs and guidance documents will be provided by the Senior Trial Coordinator to the CI and their teams to help them understand set-up of non-CTIMP research
- If required, a CCTU CTC will be allocated to the trial to work with the CI during set-up and conduct of the trial

7.2. Sponsorship

- The CI/CTC will be advised to contact the proposed Sponsor to obtain their provisional agreement to act as Sponsor. The Sponsor will usually be the substantive employer of the CI
- For externally sponsored projects, CCTU will require confirmation that they agree to Sponsor the trial in principle and where necessary obtain details of their policies and processes for the set-up and conduct of new trials

7.3. Risk Mitigation Guidance

- CCTU/GD049 CCTU led Non CTIMP Risk Mitigation Guidance should be used to consider how risks/hazards will be handled before creating the submission documents

7.4. Generation of Protocol

- The CTC will work with the CI and the trial team to generate the protocol using the appropriate template (CCTU/TPL001 or R&D/TPL005)
- It will be necessary to have input from relevant members of staff (e.g. statistician, programmer/manager, data manager, health economist, device manufacturer etc.)
- If the trial involves administration of drugs (but not as IMPs) a trial pharmacist should be consulted
- If the trial involves an intervention using a medical device, the manufacturer should review the protocol (or Clinical Investigation Plan, CIP) to assess conformity to their Technical File (TF)
- Other departments are consulted as required (e.g. radiology for imaging procedures, pathology for any trial specific blood or tissue tests, etc.)
- The final draft protocol will be reviewed and agreed by all relevant members of staff and departments, checked by the CTC for completeness and consistency with information provided in other documents (e.g. IRAS, PIS-ICF etc.) and forwarded to the trial Sponsor for authorisation

7.5. Protocol peer review

- To obtain REC approval the scientific quality of the trial must be reviewed by an independent expert in the relevant field. It is the responsibility of the Sponsor to arrange this
- Unless already completed by trial funders, the trial Sponsor will arrange for the protocol peer review
- For Cambridge Sponsored Trials, peer review can be provided by:
    - The Scientific Advisory Board

  - R&D Oncology Committee
  - The CUH Research Advisory Committee (RAC)
- The CTC or delegate will forward the final draft protocol together with a completed IRAS form to the Sponsor's office for review
- Peer review for Cambridge sponsored trials can take 4-6 weeks
- An anonymised peer review report will be sent to the CI. A copy filed in the TMF

7.6. Participant documents

- The CTC/designee will work with the CI and their team to generate/obtain all necessary participant documents (Information sheets, Consent forms, GP letter, Identification card, advertisement leaflets, invitation letters, participant facing questionnaires etc.)
- CCTU templates or HRA templates can be used for the generation of these documents. The HRA website contains detailed guidance on the design and content of participant documents
- If validated questionnaires are to be used, check the terms of use, seeking permission if necessary, and ensure funding is in place if required. Some validated questionnaires are licensed for specific use and may also require registration for use in clinical research e.g. Euroqol EQ-5D
- Both validated and non-validated questionnaires must be submitted to the REC/HRA for approval
- Final draft participant documents should be reviewed and agreed by CIs and appropriate members of their teams – the CTC will facilitate this
- It is strongly recommended that participant facing documents are sent to a patient and public panel for advice on their suitability and clarity
- The CTC or designee will ensure consistency of final documents before sending to the Sponsor, checking for:
  - Accuracy
  - Consistency with protocol
  - Adherence to CCTU SOPs and HRA guidelines
  - Use of appropriate language (lay language)

7.7. Insurance and indemnity

- Cambridge sponsored trials are covered by the NHS Clinical Negligence Scheme for CIs who are employees (substantive or honorary) of CUH. Refer to R&D/SOP005 Management of Contracts for Research Projects
- If the CI is a substantive employee of the UoC, additional insurance will be arranged to cover negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the trial
- The CTC will complete the insurance application form for human volunteer trials and submit to the UoC Insurance department at insurance.section.online@admin.cam.ac.uk
- The provisional letter of insurance must be included in the HRA submission. Confirmation of insurance must be submitted to obtain overall HRA approval, normally granted upon receipt of REC approval

- For externally sponsored trials, the Sponsor must be consulted for their requirements regarding insurance and indemnity
- The CTC will request a copy of the insurance certificate/letter. No documentation is provided for NHS indemnity
- For trials with International sites refer to CCTU/SOP064 Setting up International Sites

7.8. Trial supplies, agreements and contracts

- The CTC will work with the CI and their team to decide what trial supplies are required (for example special blood/sample tubes, drugs, devices etc) and will provide advice as to how to find suitable suppliers
- The CTC will liaise with the relevant suppliers - refer to CCTU/SOP045 Use of Vendors, or UoC equivalent if they are involved
- Any funding agreements must be reviewed by the Sponsor's legal and finance teams. Refer to R&D/SOP005 Management of Contracts for Research Projects for further details
- Only a representative of The Sponsor legal team can negotiate agreements on behalf of trials conducted through CCTU
- Only an authorised signatory as advised by legal team can sign any trial related agreements and contracts
- Before trial recruitment (but ideally earlier) all agreements and contracts must be in place. The Sponsor legal team can advise on the types of contracts that must be in place before the start of the trial, e.g. providers of trial equipment, funders, subcontractors, collaborative agreements
- A participating site agreement template should be prepared and agreed between the Sponsor's legal team and the CI/CTC
- The CTC or designee will coordinate the preparation of the contracts and agreements in collaboration with the Sponsor's legal team
- Draft contracts will be sent to all interested parties for review and approval before the final contracts are prepared and signed (CTC to check number of copies required and whether wet ink or electronic copies are acceptable)
- Fully executed contracts and agreements will be filed in the TMF and a copy sent to the Sponsor

7.9. Cambridge Sponsored Trials with International Sites

- For clinical research trials that have international sites, refer to R&D/POL003 Trust Sponsored International Studies. Typically the trial team at the country lead site in the non-UK country will take responsibility for submission to their national EC/CA bodies
- CUH Research Board approval will be required for international sites
- For trials that are jointly sponsored with the UoC, the UoC Insurance office must be contacted to provide insurance requirements and costs
- Refer to CCTU/SOP064 Setting up International Sites for further details

7.10. IRAS completion

- The submission forms for clinical research approvals are generated from the IRAS system

- The IRAS website: www.myresearchproject.org.uk provides guidance on using this application - the system is updated regularly so always check for most recent guidelines
- The CI is responsible for completing the IRAS form, but may delegate this to the CTC. The CI must review and confirm any changes required before a final draft is submitted for Sponsor review. Refer to CCTU/GD012 for IRAS completion and submission guidance
- Information entered into these forms must be complete, accurate, in sufficient detail and written in a lay language where applicable
- Relevant clinical departments and other CCTU staff should be consulted when completing parts of the IRAS form (e.g. statistician, data manager, laboratory manager, research nurse(s), pharmacist, radiology expert etc).
- For device investigations, the manufacturer should have input in the population of the medical devices form on IRAS
- The final draft of the IRAS form will be checked by the CTC for consistency with the trial protocol and supporting documentation prior to sending to the Sponsor for review

7.11. Risk assessment and monitoring plan

- A risk assessment should be carried out use CCTU/FRM112 Risk Assessment Form for NON CTIMP CCTU led trials
- This risk assessment will inform the level of monitoring.
- If monitoring is required A detailed monitoring plan can then be created use CCTU/TPL082 CCTU Led Non-CTIMP Monitoring Plan template

7.12. Setting Up Device Trials

- Clinical trials of a medical device are governed by the Medical Device Regulations and require ethical approval (they may also require authorisation by the MHRA). Drug and device combinations may have additional requirements – consult R&D.
- Refer to the current International Organisation for Standardisation (IOS) guidance for 'Good Clinical Practice in Device Investigations involving Human Subjects'
- Device trials will require review by Clinical Engineering. This can be arranged through R&D
- MHRA approval must be obtained for non-CE-marked devices where data will be used as evidence of conformity to the MDD (Medical Device Directive), or for some CE-marked devices that are the subject of an investigation outside intended use
- Note that only data from MHRA approved trials can be used in any future CE-mark applications
- For detailed guidance on the preparation and submission of applications for device trials refer to the MHRA website https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device and the HRA website
- Device submissions require PCA 1&2 forms and sterilisation annex as a minimum

- Supporting documents are produced using a combination of the device technical file (Investigator Brochure, risk analysis, instructions for use, device labels, bench testing and clinical experience to date Investigation specific documents Clinical Investigation Plan, Consent, Investigator CVs)
- The IRAS Medical Devices form is signed off by the device manufacturer prior to MHRA submission
- MHRA review will include all of the aspects that would be reviewed as a CTIMP, plus the technical aspects of the device manufacture
- The R&D department should be approached for further advice

7.13. Sponsor authorisation of all trial documentation

- The Sponsor must review and approve the complete submission package before REC/HRA or MHRA submission
- The CTC or designee will send to the Sponsor for review:
- All finalised documents required for REC submission (listed on the REC submission checklist on IRAS)
- A PDF version of the completed final draft IRAS form
- The Sponsor comments and requests for additional information will be addressed by the CTC. The revised submission package will be sent back to the Sponsor for review until all queries are resolved
- Following approval of the final documentation by the Sponsor, the CTC or designee will proceed with obtaining electronic authorisations for the IRAS form from the CI and other relevant members of staff as required (e.g. radiation expert). The final signature from an authorised representative of the Sponsor will confirm Sponsor approval

7.14. NIHR Portfolio Adoption for CRN support

- For non-commercial trials applying for NIHR portfolio adoption and CRN support, the NIHR Portfolio Application Form (PAF) is generated and submitted electronically in IRAS
- The PAF form can be submitted at any time prior to HRA submission as it does not require signatures
- The funding award letter must be submitted with the PAF
- The CI will be notified whether the trial is eligible for NIHR portfolio and CRN support. The final decision will be made following receipt of REC and HRA approvals. Unsuccessful applications can be contested
- Trials adopted by the NIHR CRN portfolio have access to NHS infrastructure for research, support for training and qualify for ISRCTN registration
- Further detail on NIHR CRN support and NIHR portfolio eligibility criteria can be found on the NIHR website

7.15. REC and HRA submission

- Refer to the HRA website for up to date guidance on HRA/REC submissions
- Refer to CCTU/GD012 Initial REC Submission Guidance for guidance on:
- Submissions
- Booking REC slots via the Central Booking System

- Receiving validation for application
- Receiving approvals

7.16. CRF design and trial database

- Once the final protocol is available, the CTC will produce a list of variables, use CCTU/TPL048 Variable List or equivalent documentation if using CRF generator. This will be reviewed and agreed by the CI and trial statistician
- Once approved the CRF design and trial specific database will start Refer to:
- CCTU/SOP049 Data Management Tools and Procedures,
- CCTU/SOP013 Paper Case Report Form Design and
- CCTU/SOP055 Using the CRF Generator to Create Tools to Capture Clinical Trial Data
- A complete set of CRFs must be available prior to trial initiation
- A data management plan should be in place refer to CCTU/TPL009 Data Management Plan before the trial begins to describe the data management activities during the course of the trial

7.17. Randomisation

- If randomisation is required refer to:
- CCTU/SOP036 Open Label Randomisation
- CCTU/SOP046 Blinded Randomisation
- CCTU/SOP053 Paper based Randomisation

7.18. Trial oversight committees

- Each trial may have a Trial Management /Group/ Trial Steering Group/Independent Data Monitoring Committee (TMG/TSC/IDMC)
- Refer to CCTU/GD026 Trial/Study Management Groups and Committees

7.19. Trials involving samples

- If the trial involves taking, processing and/or analysing samples, refer to:
  - CCTU/SOP044 Research Sample Management,
  - CCTU/SOP071 Selection of Laboratories for Analysis of Research Samples
  - CCTU/FRM108 Laboratory Self-Assessment Questionnaire

7.20. Investigator meetings

- The CTC may organise investigator meeting where all key players and collaborators come together to discuss aspects of the trial.

7.21. Approvals and documentation required before trial opening at the lead site

- For a non-CTIMP clinical research trial to start at the lead site the following must be in place as a minimum (*this is not an exhaustive list*):
- REC favourable opinion

- HRA approval
- MHRA Notice of no objection for device trials (if required).
- ARSAC approval (if required)
- Lead site confirmation of capacity and capability
- CRFs finalised and signed off
- Database designed and signed off
- Insurance arrangements in place (as required)
- Sponsorship letter (if appropriate)
- All agreements/contracts executed
- Randomisation system in place (if required)
- Trial specific SOPs and manuals (as required)
- Completed training logs for all involved in conduct of trial
- Completed Signature/Responsibility Log for all involved in the trial and their CVs (GCP certificates are recommended but not mandated)
- Localised participant documentation
- Laboratory accreditation certificates/self-assessment questionnaire
- Sample collection kits (if applicable)
- Out of hours test (refer to SOP005 if applicable)
- Medical Device tracking documents (accountability logs, inventory logs and destruction logs, as appropriate)
- TMF and ISF in place TMG/TSC/IDMC charters (if applicable)

7.22. Obtaining CUH approvals

- Approach R&D for advice regarding contacting relevant departments to obtain local CUH departmental capacity and capability approvals. Refer to
- R&D/POL005 Review and Set-Up Process for Confirming Capacity and Capability

7.23. Trial registration on public website

- All trials are expected to be registered on a publicly accessible trial register within 6 weeks of the first participant having been recruited.
- Accepted registries for non-CTIMPs:
- International Standard Randomised Controlled Trials Number register
- ClinicalTrials.gov
- NIHR Clinical Trials Gateway
- If the trial is eligible for NIHR adoption, the ISRCTN registration is provided free of charge; details of how to apply are sent to the CI following adoption approval
- ClinicalTrials.gov registration can be completed at any time by the investigator by directly accessing the website
- Registration in a public database prior to recruitment of first participant is also a condition for publication of a trial in a medical journal

7.24. TMF and filing of records

- A TMF must be generated for each trial. Refer to CCTU/SOP015 TMF and ISF Essential Document Management and CCTU/TPL032 Trial Master File Index.
- The TMF will be maintained by the CTC or designee throughout the trial duration and will be archived following the completion of the trial
- All finalised trial documents generated during the course of the trial as well as all submissions, approvals and relevant correspondence with REC, HRA and other bodies must be filed in the TMF
- For device trials, the full device Technical File should be held by the manufacturer, and this should be acknowledged appropriately in the TMF

7.24.1. Trial initiation at the lead site

- When all approvals and documents are in place the CTC will liaise with the CI to arrange initiation and opening of the lead site for recruitment. Refer to the relevant sections of CCTU/SOP024 Initiation Meeting for CTIMPs
- Once the lead site has opened the CTC will arrange the set-up and initiation of other sites.

7.25. Opening Participating sites

- Refer to CCTU/SOP039 Setting Up and Opening a Participating Site for Trust Sponsored Trials for details when opening participating sites
- Participating sites will be chosen based on receipt of a positive site feasibility assessment refer to CCTU/TPL065 Registration of Interest/Feasibility
- Following submission to HRA via IRAS and receipt of the HRA initial assessment letter, the CTC/delegate will send this letter together with the Local Information Pack (LIP) to each site, including the local research team, R&D and the local CRN
- The local R&D department will review the LIP and confirm their capacity and capability to deliver the trial at the site following HRA approval
- Each participating site must receive R&D Capacity and Capability before recruitment can begin
- Check IRAS guidance on www.myresearchproject.org.uk for requirements involving sites in devolved nations.

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.
MHRA, Good Clinical Practice "Grey Guide"
HRA website – www.hra.nhs.uk
NIHR website: www.nihr.ac.uk
IRAS website: www.myresearchproject.org.uk
MHRA website: www.gov.uk/mhra
CTA algorithm: www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk
NIHR Portfolio adoption: www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/
Clinical Trials Toolkit: www.ct-toolkit.ac.uk
UK Framework Policy for Health and Social Care Research
Medical Devices Regulations 2002 and amendments

10. Associated Documents

R&D/SOP006 – GCP Training Procedure
R&D/GD009 - CV for Research Personnel
CCTU/TPL058 - Delegation of Responsibility Log
CCTU/FRM051 – Trial Specific Training Record
CCTU/TPL002 – Patient Information and Consent Template Adults
CCTU/TPL009 - Trial Specific Data Management Plan
CCTU/TPL010 - Data Monitoring Committee Charter Template
CCTU/TPL050 - Case Report Forms Completion Guidelines Template
CCTU/TPL007 - Statistical Analysis Plan Template
CCTU/TPL027 - Trial Steering Committee Charter
CCTU/TPL030 - Monitoring Plan

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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