Standard Operating Procedure CCTU/SOP047

CTIMP Start-up/Set-up Procedures for Trial Teams

1. Scope

This SOP must be followed by trial teams running CTIMPs where QA and QC responsibility for Sponsor oversight has been delegated or contracted to the Cambridge Clinical Trials Unit (CCTU).

2. Purpose

To describe the procedures from funding award to Lead Site Activation to ensure that:

- Trials are organised and opened in accordance with CCTU, Regulatory, Research Governance and GCP requirements
- Investigators are fully informed of their responsibilities and that staff involved in the set-up of a CTIMP are aware of the trial requirements

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 CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Sponsor	An individual , company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial
Trial Team	Generally includes the Chief Investigator (CI), Principal Investigator (PI), Clinical Trials Coordinator (CTC), Data Manager (DM) Research Nurse at the coordinating site as identified and delegated by the CI and/or Sponsor
Regulatory Team	Includes the Clinical Trials Officers (CTOs), Regulatory and Quality Manager, Clinical Trials Monitors (CTMs) and the Pharmacovigilance (PV) Officer(s)

3.2. Abbreviations

Abbreviation	Meaning
ARSAC	Administration of Radioactive Substances Advisory Committee
C&C	Capability & Capacity
CCTU	Cambridge Clinical Trials Unit

CI	Chief Investigator
CRF	Case Report Form
CRS	Combined Review Service
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTM	Clinical Trials Monitor
CTO	Clinical Trials Officer
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Approval System
LIP	Local Information Pack
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PI	Principal Investigator
PV	Pharmacovigilance
R&D	Research and Development
REC	Research Ethics Committee
RFI	Request for Information
SAF	Study Assessment Form
SoECAT	Schedule of Events Cost Attribution Tool

4. Undertaken by

Members of the Trial Team as delegated by the CI

5. Items Required

- CCTU/SOP024 Initiation Meetings for Sponsored CTIMPs
- CCTU/SOP040 Risk Assessment Process for CTIMPs
- CCTU/SOP045 Use of Vendors
- CCTU/GD029 CTIMP Submission Checklist
- CCTU/TPL001 Protocol Template
- CCTU/TPL002 Patient Information Sheet and Consent Template
- CCTU/TPL014 Participant ID Card Template
- CCTU/TPL015 GP Letter Template
- CCTU/TPL017 Patient Information and Consent Template 11-15 Year Olds
- CCTU/TPL070 GP Letter Pregnant Partner Template
- CCTU/TPL079 Pregnant Partner PIS & ICF Template
- CCTU/FRM001 Serious Adverse Event Report Form
- CCTU/FRM003 Pregnancy Report Form
- CCTY/FRM004 Other Important Safety Issues Reporting Form
- CCTU/SOP005 Test of Out of Hours Medical Cover Arrangements
- CCTU/TPL087 Out of Hours Test File Note
- Study Assessment Form (available from the Cambridge R&D Department)

6. Summary of Significant Changes

Review by statistical and pharmacy departments to occur before initial submission to the regulatory team.

Draft CRS applications no longer needs to be transferred into a word document for CTO review.

Trial teams will generate and provide PV forms to the PV Team.

The trial team will perform the out of hours test for the lead site.

7. Method

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

7.1. Initial Notification

- Once a trial has received funding, the following departments should be notified of the start of trial set-up activities:
    - CCTU
    - Pharmacy
    - Relevant Legal Team (R&D and/or University)
    - Any other essential department involved in the set-up of the trial (e.g. laboratories)

7.2. Documentation Generation

- The relevant SOPs, templates, forms and guidance documents to enable the generation of trial level documentation are available in Q-Pulse
- Templates listed in Section 5 are mandated for Cambridge Sponsored trials as appropriate. Editable copies can be requested from the CCTU for staff without access to Q-Pulse
- The trial team are responsible for developing the essential documents using the templates provided and interacting with the relevant departments/staff as necessary to ensure that the relevant information is included (e.g. radiology for timing and duration of scans etc.)
    - CCTU/GD029 CTIMP Submission Checklist should be used as a guide for the documentation required
    - A trial specific R&D Number should be requested from the relevant R&D contact
- When required:
    - Insurance provision must be sourced by the trial team and confirmation of provisional cover provided as part of the submission
    - The Accord Specialist will provide guidance with the final cost attribution detailed in SoECAT (from April 2023 an online SoeCAT form is available to use)
- Before the initial submission review by the Regulatory team. Where appropriate:
    - The CCTU Statistician will provide statistical information required for the protocol and the IRAS Combined Review Service (CRS)

        - The relevant pharmacy department will provide input into:
            - The IMP sections of the protocol,
            - The Medicines Information questions in the CRS application
            - The IMP labels
    - The Study Assessment form (SAF – available from Trust R&D) must be signed by the appropriate Divisional Lead for the CI/PI department(s)

7.3. Protocol Peer Review

- The scientific quality of the trial must be reviewed by an expert in the field who is not involved in the trial
- Note: Review of the trial as part of a programme grant does not constitute sufficient peer review of the protocol, an additional peer review will be required
- Peer review can take up to 6 weeks to complete
- Peer review should happen in advance of CCTU review of the submission documentation, however it can happen in parallel if appropriate
- Liaise with the R&D Department to arrange for a suitable peer review of the protocol if not already completed by external funders charities or sponsors

7.4. Trial Supplies, Agreements & Contracts

- Refer to CCTU/SOP045 Use of Vendors
- Once a supplier has been identified, the trial team must liaise with the relevant legal team to ensure that service level agreements are negotiated and implemented (including technical agreements, etc.) as required
- The CTO requires a copy of all draft agreements and any relevant site-level documents (e.g. Organisation Information Document) as part of the review process
- All funding agreements relating to the supply of IMP, equipment, services and facilities must be reviewed by the relevant legal team
- Only a representative of the relevant legal team can negotiate agreements on behalf of trials conducted through the CCTU
- Only an authorised signatory as confirmed and obtained by the relevant legal team can sign any trial related agreements
- A copy of all final executed agreements should be provided to the CTO by the trial team

7.5. Initial Submission Review

- All submission documentation must be submitted to the CTO as a single package, to allow essential cross-checks to be conducted
- The trial team should contact any reviewing departments prior to submission to the CCTU so they are prepared to answer any queries which may arise during the Regulatory Team review process e.g. Laboratories, Clinical Engineering etc.
- Once the Collaborative Research Letter has been signed and executed by all parties the CTO will begin the review process

- The CTIMP Submission Checklist CCTU/GD029 should be used as a guide for the documentation required for review by the regulatory team
    - If any document listed in the submission checklist is not required, this should be indicated and explained in the submission email
    - HRA Technical Assurance review documentation should be submitted to the CTO (pharmacy & radiation)
    - Appropriately signed SAF for CI/PI department(s) should be submitted to the CTO.
- Once all documentation is submitted, a submission validation email will be sent to the trial team, confirming the documentation received, version numbers, dates and the timelines for review and feedback
- The documentation will be reviewed:
    - For regulatory compliance (MHRA, REC, HRA and ARSAC)
    - Against recent Grounds for Non-Acceptance and reported Serious Breaches (MHRA) in other trials
    - Against recent HRA and REC concerns and released guidance
    - With a view to incorporating risk mitigation early in trial documentation
- All changes required following the regulatory team review will be returned where possible, using tracked changes to allow the trial team to review and agree changes in a timely manner
- Once any agreed changes are made, the CTO will provide authorisation for the submission to the regulatory authorities

7.6. Risk Assessment

- During/following initial review of the trial documentation the CTO will commence the risk assessment and mitigating action process in accordance with CCTU/SOP040

7.7. NIHR Portfolio Adoption

- Applications for NIHR CRN support are made via the new part of IRAS through the Combined Review Service (CRS) application.
- The trial team must send confirmation to the local R&D department once their trial has been adopted into the NIHR Portfolio

7.8. HRA/REC and MHRA Submission (via the CRS)

Copies of all related correspondence should be forwarded to the CTO in a timely manner.

- The HRA/REC/ MHRA submission can only be made once:
    - The CTO has confirmed that the review is complete and all required changes have been made to the CRS application and trial documentation
    - All necessary documents have been signed/authorised by the relevant parties
    - The CTO is sent the final trial application from the trial team via the CRS system to make the final submission

- The trial team applicant who transferred the final application for submission to the CTO will receive notification to make a REC meeting. This notification and related correspondence will only be sent to the individual who sent the final application to the CTO (others including the CI or other added collaborators will not receive notifications). As such, that individual must be available to respond to correspondence and notifications promptly
- Any Request for Information (RFI) required by the HRA / REC / MHRA to the application or submitted documents must be reviewed and agreed before re-submission by the CTO

7.9. ARSAC Submission

- The ARSAC submission can only be made once:
  - The CTO has confirmed the review is complete
  - The necessary signatories have signed the ARSAC form electronically. (this form is located in the standard IRAS website Part B Section 3)
  - The form is then uploaded as a Project Document to the CRS application in the new part of IRAS (document type: Miscellaneous: Non MHRA Only)

The submission must be copied to the CTO via cuh.ccturegulatory@nhs.net

7.10. CRF Design, Trial Database & Randomisation System

- The trial team are responsible for engaging the Data Manager/ Programmer as appropriate for the generation of the trial specific CRF, database and/or randomisation system
- The Data Manager/Coordinator/Programmer, as appropriate will work with the trial team to generate and finalise the CRF and randomisation system in advance of the trial initiation meeting
- The Data Manager/Programmer as appropriate is responsible for the generation of the trial specific database and associated documentation in accordance with CCTU SOPs and the timelines set out in the risk assessment mitigating actions

7.11. Site-specific Document Submission

Upon receipt of consolidated MHRA, HRA & REC validation, the trial team must submit the following to the Cambridge R&D department

- The Local Information Pack (LIP)
- The signed SAF for the CI/PI department(s)

The LIP should not be sent to participating sites until after the lead site submission has been made

7.12. HRA/REC/MHRA & ARSAC Approvals

- Once received, all approval documentation must be forwarded in a timely manner to the CTO for inclusion in the Sponsor file
- Note: A requirement of REC approval is that the trial must be registered on a publicly accessible and searchable database

- The HRA will automatically add all CTIMP trials of new medicines approved in the UK to the ISRCTN registry (from Jan 2022), and the record must be maintained by the trial team
- For Non CTIMP trials of new medicines approved in the UK, check the HRA registry with ISRCTN for the trial type and if not available, the trial team will be required to complete the registration
- For trials included on the NIHR portfolio the trial will automatically be included as part of the adoption process on the www.crn.nihr.ac.uk website
- Some disease indications may have specific websites where the trial should also be registered
- The use of automated reminders for annual reporting deadlines are strongly recommended. Trial teams can utilise the ReDA alert system or any alternative system they feel appropriate.

7.13. Pre Initiation

- Lead site C&C approval will be provided directly to the trial team by the R&D Department
- Documentation generated as part of the risk assessment mitigating action requirements must be sent to the CTO for review and confirmation ideally at least 2-3 weeks in advance of the initiation meeting. Near final copies of certain documents (charters / manuals) may be provided for review prior to initiation following discussion with the CTO
- Once all mitigating action documentation is agreed the initiation meeting can proceed
- The trial team will conduct the lead site test of out of the hours medical cover arrangements in accordance with CCTU/SOP005 then generate and provide the CTO with a copy of file note CCTU/TPL087 Out of Hours Test File note demonstrating a successful test
- The trial team will generate and provide the trial specific PV forms to the PV Officer for review. The PV Officer will approve and finalise these for use in the trial
- Any outstanding documentation for the sponsor file will be requested and should be provided prior to the initiation meeting in order for the meeting to proceed

7.14. Initiation Meeting

Refer to CCTU/SOP024 Initiation Meeting for Sponsored CTIMPs

7.15. Lead Site Activation

- The CTO will provide the trial team with the email confirmation of site activation when all pre-trial procedures and initiation requirements have been met
- No trial interventions can be undertaken until the activation confirmation has been provided by the CTO

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"

10. Associated Documents

R&D/POL003 International Studies Policy

R&D/SOP001 CTIMP Delegation of Roles and Responsibilities

CCTU/SOP041 Green Light Procedure for IMP Release

CCTU/SOP002 Pharmacovigilance for Trial Teams

CCTU Collaborative Research Letter

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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