

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 Participating 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
in Vitro Diagnostic Device	<p>IVD medical devices are tests used on biological samples, such as tissues, blood or urine, to determine the status of a person's health.</p> <p>This may be a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination; and is intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information.</p> <p>A companion diagnostic device is an IVD device, which is essential for the safe and effective use of a corresponding medicinal product to: identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.</p>

	For guidance and definitions see: Clinical trials that include an in vitro diagnostic device - GOV.UK
Modification of an Important Detail	Modifications (formally termed amendments) that do not significantly impact the safety or rights of the participants, but the authorities need to be aware of them for administrative or oversight purposes. Instructions for notifying the authorities about a modification of an important detail are provided on completion of the Modification Tool
Notification Scheme	MHRA Scheme that enables a more streamlined and risk-proportionate approach to processing CTA for 'initial' applications. The scheme only applies to Phase 4 and certain Phase 3 clinical trials deemed to be of lower risk and there are no documentation exemptions when applying to this scheme
Public Registry	A primary or partner registry of, or a data provider to, the WHO International Clinical Trials Registry Platform, provided that the registry, or the data provider, facilitates public access to information about the trial in the United Kingdom
Participating Site	Referred to in the regulations as a 'Trial Location' currently defined as: a hospital, health centre, surgery or wider healthcare setting, or facility or premises at or from which a clinical trial, or any part of such a trial, is conducted. For the purposes of CCTU SOPs, Forms and Templates, this does not include Participants homes.
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 participating 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
CtQ	Critical to Quality
DB	Database

GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IQM	Ideagen Quality Management
IRAS	Integrated Research Approval System
IVD	In vitro diagnostic device
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/GD073 Critical to Quality Factors Guidance
- CCTU/FRM129 Critical to Quality Factors Form
- CCTU/SOP045 Use of Vendors
- CCTU/GD029 CTIMP Submission Checklist
- CCTU/TPL001 Protocol Template
- CCTU/TPL002 Participant Information Sheet and Consent Template
- CCTU/TPL014 Participant ID Card Template
- CCTU/TPL015 GP Letter Template
- CCTU/TPL017 Participant 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
- CCTU/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
- CCTU/TPL112 Inclusion and Diversity Plan
- Study Assessment Form (available from the Cambridge R&D Department)

6. Summary of Significant Changes

Addition of Critical to Quality Factors section and Form requirement

Inclusion and Diversity Plan added to list of required documents

NIHR Research Delivery Network support and Portfolio adoption process updated

Widespread updates in response to the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538

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. Gantt Chart

A Gantt chart is to be produced by the CTC at the start of a project, typically after the funding is approved. A copy of the Gantt chart is to be sent to the Regulatory Team for review.

It should include all key tasks needed to complete the trial such as timelines for (not an exhaustive list):

- Preparation of trial submission documentation (include PPI and Peer review)
- Sponsor review and then regulatory authorities, submission and approval
- Preparation of all other essential documents (risk management, monitoring plans, trial manuals, CRF/DB design etc)
- Database build and testing
- The staggered set up and opening of participating sites and associated incremental participant accrual to reflect that, in practice, participating sites will not all open at the same time
- Recruitment phase
- Close down phase (data cleaning, query resolution, DB lock and analysis)
- Closing down of participating sites
- End of Trial Reporting and Publications

The Gantt chart is to be maintained throughout the lifecycle of the trial and discussed as part of TMG meetings and any other relevant trial meetings (e.g. TSC Meetings).

7.3. Submission Requirements

7.3.1. Pre-Submission Considerations

The following should be undertaken before submission to the CCTU Regulatory Team if applicable to the trial. Some processes are lengthy and should begin early in trial set-up so that they do not impact negatively on trial timelines.

Information and procedures continue to evolve in response to the implementation of new the Clinical Trial Regulations (2025) and ICH-E6(R3), so please check websites for up-to-date information and detail specifics

- If the trial intends to submit under the MHRA Notification Scheme this should be clearly indicated in the initial submission covering letter and a copy of the MHRA [Inclusion and exclusion criteria Form](#), available from the MHRA website, must be provided to the CTO as part of the CCTU Regulatory Team initial submission. The relevant Pharmacy Department should also be made aware of this decision and confirmation of their agreement provided. Refer to website, [Clinical trials for medicines: notifiable trials - GOV.UK](#)
- If an SmPC is being used for an IMP, the trial team must confirm they have reviewed the suitability of section 4.8 of the SmPC for use as the RSI. For example, assess that the terms within this section are clearly described in the MHRA expected RSI format and terms are coded to MedDRA. Refer to website for full details: [Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK](#)
- In cases where a trial includes use of an in vitro diagnostic (IVD) device, including companion diagnostic devices, refer to MHRA guidance on their use in CTIMPs: [Clinical trials that include an in vitro diagnostic device - GOV.UK](#)
- For trials that intend to use data registries, such as NHS England Data & Research Services or other specialized and regional registries (e.g. NIHR Bioresource) initial agreement discussions should begin early and confirmation should be sought on what registry specific requirements are needed in participant documents e.g. PIS and ICF and that registry data can be used in accordance with funder agreements e.g. clinical trial data repositories, publications etc)
- For trials requiring expert advice: check the website for a non-exhaustive list of circumstances in which expert advice may be needed, and the timelines and information required to arrange this. Note, expert advice meetings occur long in advance of the actual clinical trial submission, [Clinical trials for medicines: expert advice - GOV.UK](#)
- For multi-centre trials,
 - The Accord Specialist will provide guidance with the final cost attribution detailed in the online SoECAT. Visit: [Online SoECAT Guidance | NIHR](#)
 - Technical Assurance Forms (pharmacy and radiation) should be submitted for a review by authorised HRA registered assessors before submission to the CCTU. This can take up to 3 weeks

7.4. Documentation Generation

- The relevant SOPs, templates, forms and guidance documents to enable the generation of trial level documentation are available in IQM (formally 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 IQM
- 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
- Before peer review, where appropriate:
 - The trial 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 IRAS application
 - The IMP labels (For current MHRA guidance on IMP and NIMP labelling see, [Clinical trials for medicines: labelling - GOV.UK](#))
- Before submission to the Regulatory Team:
 - Ensure the initial submission cover letter contains all the necessary requirements outlined on the MHRA website and all necessary documents are part of the submission package, [Clinical trials for medicines: apply for approval in the UK - GOV.UK](#)
 - The trial team should have reviewed the MHRA guidance regarding [common issues with validation and assessment of clinical trial applications and how to avoid them](#) and considered all relevant aspects for the submitted documentation
- The Study Assessment form (SAF – available from Trust R&D) must be signed by the appropriate Divisional Lead for the CI/PI department(s).

7.5. Critical to Quality Factors

- During the initial design and set-up stage (development of the protocol, PIS-ICF, IRAS form etc), the trial team will identify Critical to Quality (CtQ) factors and document them in CCTU/FRM129 Critical to Quality Factors form
- The CtQ Factors form (CCTU/FRM129) and associated guidance (CCTU/GD073) are intended to support trial team discussions and decision-making about what aspects of the trial are critical to generating reliable data

and protecting the safety of research participants, and facilitate a quality by design proactive approach to the trials' design

- The final draft of the CtQ Factors form will be submitted to the CTO with the initial submission package
- The CtQ Factors form must be finalised prior to submission to the regulators

7.6. 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
- 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

7.7. 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 participating 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
- The Collaborative Research Letter should ideally be signed by all parties prior to submission

7.8. 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.
- 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

- 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 CTO 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
 - Trial teams will have a maximum of 4 weeks to provide their response to the regulatory team review. If the 4-week timeline is exceeded trial review will be de-prioritised
- Once any agreed changes are made, the CTO will provide authorisation for the submission to the regulatory authorities

7.9. Risk Assessment

During/following initial review of the trial documentation the CTO will finalise the CtQ Factors form with the trial team prior to the submission to the regulators, then commence the risk assessment and mitigating action process in accordance with CCTU/SOP040

7.10. NIHR Research Delivery Network Portfolio Adoption

- Applications for research delivery network support and inclusion on the Portfolio are not automatically submitted to the Research delivery network by selecting 'yes' in the CRS IRAS application. For details on how to apply for support visit the [NIHR website](#)
- The trial team must send confirmation to the local R&D department once their trial has been adopted into the NIHR Portfolio

7.11. 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, including the final CtQ Factors form, have been signed/authorised by the relevant parties

- The CTO is sent the final trial application with all documents approved for the submission prior to the trial team uploading them in the CRS system
- Following upload of all trial documents in CRS, the application must be routed to the Sponsor CRS system for Sponsor authorisation before it is automatically sent to the regulators for their review. Notifications are not issued in CRS so the trial team must inform the CTO when they have requested sponsor authorisation in CRS
- Once the CTO has confirmed the submission in CRS, the trial team applicant (Project Deputy in CRS) 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

7.12. 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

7.13. 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 and mitigating actions plan

7.14. Participating 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 participating site submission has been made

7.15. 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: It is a legal requirement that the trial be registered on a public registry
 - The HRA will automatically add all CTIMP trials of new medicines approved in the UK to the ISRCTN registry and the record must be maintained by the trial team
 - The trial team will notify the authorities of the date the trial registry went live. This will occur when the trial team submits a modification of an important detail to notify the authorities of the date the trial recruited (consented) the first participant
 - For trials included on the NIHR portfolio the trial will automatically be included as part of the adoption process <https://www.nihr.ac.uk/isrctn-registration>
 - Some disease indications may have specific websites where the trial should also be registered
 - The use of automated reminders for DSUR reporting deadlines are strongly recommended. Trial teams can utilise the ReDA alert system or any alternative system they feel appropriate.

7.16. Pre Initiation

- Lead participating 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 participating 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/TPLO87 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

7.17. Initiation Meeting

Refer to CCTU/SOP024 Initiation Meeting for Sponsored CTIMPs

7.18. Lead Participating Site Activation

- The CTO will provide the trial team with the email confirmation of lead participating 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
- The trial team must notify the Regulatory Team of the first participant, first visit. The trial team will then submit a modification of an important detail to the regulators with the date of the first participant recruited (consent) as well as the date the trial public registry went live

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

Common Abbreviations and Definitions CCTU/INF001

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, UKSI 2025/538, [The Medicines for Human Use \(Clinical Trials\) \(Amendment\) Regulations 2025](#)

[Clinical trials for medicines: apply for approval in the UK - GOV.UK](#)

ICH guidelines E6(R3), [ICH E6\(R3\) Step4 FinalGuideline 2025 0106.pdf](#)

[ICH guideline E8\(R1\) Step 2b on general considerations for clinical studies](#)

MHRA Website: [common issues with validation and assessment of clinical trial applications and how to avoid them](#)

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

Critical to Quality Factors Principles Document: https://ctti-clinicaltrials.org/wp-content/uploads/2021/07/CTTI_QbD_Workshop_Principles_Document.pdf

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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