Standard Operating Procedure CCTU/SOP039

Set up and Activation of Participating Sites for Cambridge Sponsored CCTU Led Clinical Trials

1. Scope

This SOP applies to multi-centre Cambridge Sponsored clinical research trials both CTIMPs and non-CTIMPs. For non-CTIMPs, the MHRA sections are not relevant. This SOP does not apply to commercially sponsored trials or research sponsored by an external non-commercial organisation.

2. Purpose

This SOP describes the process of setting up and activation of Participating Sites (PS) for participant recruitment in accordance with GCP and applicable legislation

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) jointly with Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Multicentre Trial	A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator
Participating Trial Site	The location(s) where trial related activities are conducted (referred to in this SOP as the site)
Site Information File	A sub-section of the TMF and contains Sponsor essential documents relating to an individual Participating Trial Site.
Investigator Site File	A file containing trial and site-specific essential documents located at the Participating Trial Site and maintained by the local Principal Investigator and local site research team
CTIMP	An investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of

	ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.
Non-CTIMP	A research study in humans that does not involve an IMP and does not fall in the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 Non-CTIMPs can include observational studies, interventional studies, randomised controlled studies and device studies.
Site Activation	The point at which a Participating Trial Site is opened for recruitment

3.2. Abbreviations

Abbreviation	Meaning
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CRF	Case report Form
CUH	Cambridge University Hospitals NHS Foundation Trust
DN	Devolved Nation (Scotland, Wales, Northern Ireland)
CTA	Clinical Trial Authorisation
CTC	Clinical Trials Coordinator
CV	Curriculum Vitae
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HCRW	Health and Care Research Wales
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
LIP	Local Information Pack
MHRA	Medicines and Healthcare products Regulatory Agency
mNCA	model Non-Commercial Agreement
OID	Organisation Information Document
PI	Principal Investigator
PIS	Participant Information Sheet
PS	Participating Site
PSA	Participating Site Agreement
PSF	Pharmacy Site File
REC	Research Ethics Committee
R&D	Research and Development
RoIF	Registration of Interest/Feasibility Template
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SoE	Schedule of Events
SoECAT	Schedule of Events Cost Attribution Template
TMF	Trial Master File
UoC	University of Cambridge

4. Undertaken by

Chief Investigators (CI), Principal Investigators (PI), Clinical Trial Coordinators (CTC) and other delegated members of the trial team.

5. Items Required

- CCTU/TPL028- Participating Site Activation Letter
- CCTU/TPL033- Investigator Site File Index
- CCTU/TPL034- Site Information Index in the TMF
- CCTU/TPL038- Local Pharmacy Site File Index
- CCTU/TPL058 Delegation of Responsibilities Log
- CCTU/TPL065 Registration of Interest/Feasibility Assessment Template
- CCTU/TPL087 Out of Hours File Note
- CCTU/TPL089 Non-CTIMP trial initiation form
- CCTU/FRM051 Trial Specific Training log
- CCTU/FRM064 Participating Site Initiation Check List
- CCTU/FRM086 Participating Site Initiation Form
- CCTU/SOP005 Test of Out of Hours Medical Cover Arrangements
- CCTU/SOP014 Amendment Management of CTIMPS by Trial Teams
- CCTU/SOP024 Initiation Meeting for CTIMPs
- CCTU/SOP071 Selection of Laboratories for Analysis of Research Samples
- CCTU/SOP076 CCTU Led non-CTIMP Initiation meeting procedure
- R&D/SOP005 Management of Contracts for Research Projects
- R&D/GD009 CV for Research Personnel
- Participating Site Agreement (PSA) from Trust R&D

6. Summary of Significant Changes

Addition of Out of Hours testing

Addition of reference to the International Studies SOP

Addition of reference to the Selection of Laboratories for Analysis of Research Samples SOP

Addition that site should be reminded to send the coordination team updates to out of hours procedures/contacts.

Changes to LIP, to include Schedule of Events (SoE) /Schedule of Events Cost Attribution Template (SoECAT)

Clarification of R&D requirement for electronic signatures

Clarification that 70day timeline to first recruited participant is reported on but no longer universally mandated by HRA.

7. Method

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

7.1. Identification and Feasibility Assessment of New Sites

- If an international (non-UK) site is under consideration, then refer to CCTU/SOP064 Setting up International Studies and the associated documents
- Potential participating site(s) and Principal Investigator(s) approached or expressing an interest in participating in the trial will be asked to complete a registration of interest/ feasibility assessment form (CCTU/TPL065) in order to establish their site's suitability. Potential PS will require as a minimum a copy of the trial protocol.
- The CI and CTC will review the completed CCTU/TPL065 to establish:
    - The ability of the site to identify a suitable number of potentially eligible participants
    - If the site has sufficient resources and staff with the relevant skills, expertise and time to conduct the trial procedures
    - If the site has appropriate equipment and facilities, e.g. accredited laboratories, freezer storage for samples, aseptic unit for IMP preparation
    - If the site is participating in other clinical trials that are competing for the same trial population
    - If there are any financial implications or other factors that may affect the conduct of the trial at the site
- The CTC will confirm in writing to the PI whether their site can become a PS. If the site is unsuitable to host the trial the CTC will explain the reasons for the decision
- A copy of the completed RoIF -CCTU/TPL065- and any related correspondence will be filed in the TMF for both accepted and declined sites
- A list of proposed participating sites including the PI name and qualifications will be included in the IRAS application forms for submission to HRA/REC and MHRA (HRA Approval encompasses HCRW Approval). For proposed sites in Northern Ireland and Scotland please refer to the IRAS guidance)
- Following HRA/REC and MHRA approvals for the trial the addition of further sites (not included in the original submissions) will require an amendment (see section 7.12)
    - For CTIMPS this will be a substantial amendment
    - For non-CTIMPS it will be a non-substantial amendment

7.2. Setting up NHS Sites in the UK

- Following submission to REC/MHRA/HRA trial related documents can be sent to the PS to begin their set-up process
- The Local Information Pack (LIP) will be sent to the site by the CTC, including either the HRA Initial Assessment Letter or the HRA Approval Letter (depending on timing of PS set up).
- The CTC/delegate should discuss the submission of the LIP with the PS R&D department and research team prior to submission.
- Early discussion of trial finances, including excess treatment costs, if applicable, with the PS (and PS pharmacy team) is crucial for timely site activation.
- The LIP will typically include the following (always check HRA guidelines for updates to the required contents of the LIP)
    - Copy of the IRAS Form (combined REC and R&D form) as submitted for HRA approval
    - Submitted protocol (and amendments)
    - Participant information sheet and informed consent documents (without local logos/ headers)
    - Delegation of Responsibilities Log
    - Relevant NHS model agreement
    - Localised Organisation Information Document (OID) and Schedule of Events (SoE) /Schedule of Events Cost Attribution Template (SoECAT) obtained from the HRA website (including known information)
    - Any other documents that the Sponsor wishes to provide to the site to support the set up and delivery of the trial
    - Copy of HRA Initial Assessment Letter (if one is issued) and (when issued) HRA Approval Letter and final documents
- When HRA approval has been issued:
    - The PS (PI. Local team, local R&D office and Local Clinical Research Network (where relevant) will be sent the relevant approval letters together with any revised trial documents
    - The PS will provide confirmation of their capacity and capability to deliver the trial and exchange fully executed agreements

7.3. Setting up non-NHS sites in the UK

- A Non-NHS/HSC Site Assessment Form should be completed in IRAS and submitted for each non-NHS/HSC site with the initial submission to the REC.
- The CTC to liaise with each non-NHS/HSC site about their arrangements for issuing management permission.

7.4. Participating Site Agreement

- A Participating Site Agreement (PSA) between the Sponsor and each PS will be issued, signed and filed in accordance with R&D/SOP005 - Management

of Contracts for Research Project. The mNCA template is normally used for the PSA.

- The draft agreement should be sent to the R&D department of the PS for their review before signatures are obtained
- If the R&D department of a PS has any issues with the PSA, this will be resolved between the solicitors and/or contract managers of the Sponsor and the PS R&D department, with the support of the CTC.
- For CTIMPs: A pharmacy appendix to the PSA will be completed and signed by the PS Pharmacy Department
- For non-UK sites the CUH contracts officer should be contacted for advice on the required agreements
- Please note that the current mNCA version also includes a PI declaration section to be signed and dated by the PI.

7.5. Site File Preparation

- For each participating site an Investigator Site File (ISF) will be prepared according to CCTU/TPL033 Investigator Site File Index (ensure that the approved version of the Reference Safety Information (RSI) applicable for the trial is included as detailed in the index)
- For CTIMPS, a Pharmacy Site File (PSF) should also be prepared according to CCTU/TPL038 Local Pharmacy Site File Index
- These two files should be sent to the PS prior to the Site Initiation as they contain trial and site related essential documents
- The CTC will prepare and maintain a Site Information File section of the TMF for each PS according to CCTU/TPL034 – Site Information Index in the TMF
- Any updated trial related documentation sent to PS should be filed in the ISF and/or PSF as appropriate by the PS staff

7.6. Trial Documents generated by the Participating Site

- The PS must complete the Delegation of Responsibilities Log CCTU/TPL058 provided to them by the CTC listing personnel involved in the trial at the site (PI and any Co-Investigators, Research Nurses, Pharmacist(s), Trial Coordinators, Data Managers etc, as applicable)
- Each person listed on the site Delegation of Responsibilities Log will list the duties being delegated to them with a start date and sign and initial the log prior to undertaking any trial-related duties
- The PI will sign and date every entry on the Delegation of Responsibilities log to confirm the staff suitability for their delegated responsibility
- At the point of site activation, a current CV (signed and dated, see R&D/GD009 for CV date requirements.) and evidence of GCP training must be provided for the PI and other key members of the trial team listed on the Delegation of Responsibilities log. Local staff undertaking any trial related activities at any time during the trial must be entered into the Delegation log and their CVs and GCPs sent to the CTC as appropriate
- GCP training should be updated every two years or in accordance with the PS local policy. Local policy also applies to non UK sites

- A copy of all participant documentation (PIS, ICF, GP letter etc) with site specific logos must be sent back to the CTC for checking and filing in the Site Information File of the TMF
- The completed Delegation of Responsibilities Log, CVs and GCP certificates will be filed in the ISF at the PS with copies sent to the CTC for filing in the Site Information section of the TMF
- Trial staff at the PS will be reminded that they are responsible for keeping the delegation log, CVs and GCP certificates and trial specific training logs up to date during the course of the trial

7.7. Laboratory and Pharmacy Documents

The PS should provide the CTC with:

- Accreditation documents for the laboratories that the site will be using for the trial, with their normal reference ranges
- Non accredited laboratories should be validated as per CCTU/SOP071 -Selection of Laboratories for Analysis of Research Samples SOP
- Copies of local SOPs (e.g. pharmacy) and policies that differ from those described in the trial protocol

7.8. Drug/IMP Supply System (if applicable)

The CTC will supply all PS the following as required:

- Trial specific guidelines on the drug/IMP management
- The current IB and/or SmPC for the medicinal product(s) to be used and for RSI (for pharmacy IMP management purposes)
- Trial specific prescriptions and forms for drug/IMP accountability (the Sponsor trial Pharmacist is involved to provide final approval of these documents before distribution to PS.
- Delegation of Responsibilities log, patient log etc for the site pharmacy trial file (PSF)

The Sponsor's Clinical Trials Pharmacist (Oncology or Central Pharmacy) will be involved in the preparation of the trial specific drug/IMP management guidelines. These must cover as a minimum the following topics:

- Procedures for drug supply/ordering
- Instructions for drug storage
- Instructions for preparation and administration of drug
- Drug labelling (if relevant)
- Procedure for temperature deviations
- Quarantine procedure
- Drug accountability and form completion
- Drug destruction instructions
- List of pharmacy forms provided by the Sponsor
- Pharmacy staff training requirements
- Electronic-Prescribing (if relevant)

NOTE: The trials pharmacy at the PS will be responsible for receipt, storage and accountability of the drug and for issuing the green light for the drug to be used at the site.

If the PS has its own pharmacy templates for use in the trial (e.g. prescriptions, drug accountability logs etc,) the CTC must ensure that these meet the min CCTU requirements.

7.9. Local Service Agreements

The CTC should remind PIs at PS that they must liaise with any local service departments needed for trial specific procedures (e.g. radiology, pharmacy, laboratories) as soon as the PS start-up process commences. This will ensure resources and/or agreements are in place in good time before site initiation and avoid delays in site activation.

7.10. Site Initiation

- Site initiation of a PS can only take place after the lead site has been activated
- PS initiation must be conducted before the site is activated. Its purpose is to explain all aspects of the trial to key personnel at the site (PI, Research Nurse(s), Pharmacist, Trial coordinators, Data Managers etc) and to clarify any issues that they may arise
- The site initiation process is described in detail in CCTU/SOP024: Initiation Meeting for CTIMPs and in CCTU/SOP076: CCTU led non-CTIMP Initiation meeting
- If the pharmacy team is unable to attend the PS initiation, a separate pharmacy initiation can be arranged prior to PS activation.

7.11. Site Activation

A PS can only be activated when:

- The lead site has been activated
- The local R&D department has provided the fully executed PSA and confirmation of their capacity and capability
- All items on the PS initiation checklist (CCTU/FRM064) are in place and copies of all site related documentation have been sent to the CTC for checking and filing in the Site Information File (SIF)
- A successful Out of Hours Medical Cover test has been performed refer to CCTU/SOP005 Note: Out of Hours testing is mandatory for CTIMPs; for non-CTIMPs it will be performed only if required
- For CTIMPs the completed PS Initiation checklist (CCTU/FRM064) and the Out of Hours File note (CCTU/TPL087) should be sent to the CCTU Regulatory team for review and authorisation PRIOR to site activation.
- Site Initiation has been completed and the Participating Site Initiation form (CCTU/FRM086 for CTIMPs, CCTU/TPL089 for non-CTIMPs) has been signed by the PI and CTC

- For CTIMPs/trials involving drug, the CTC will need to authorise the release of drug to the PS and the site pharmacy must give the green light for the drug to be used before the site is activated
- Arrangements for IMP receipt, storage and accountability are in place

The CTC will:

- Issue and send an activation letter (CCTU/TPL028) to the PS to inform them that their site is officially open to participant screening and recruitment
- Provide the site with a copy of the completed Out of Hours Test (CCTU/TPL087) to file in the ISF.
- Inform other relevant parties (e.g. randomisation office, contracted service providers) of the new PS activation; for CTIMPs the CTC will inform the IMP supplier to authorise release of IMP to the new site; where used forward the paper concealment list to PS.
- Remind the site PI of the need to provide relevant training on the trial protocol and procedures to all new personnel joining the trial team after the site initiation and that the Trial Specific Training Log (CCTU/FRM051) is updated and a copy sent to CTC.

During the course of the trial PS must provide the CTC with:

- Updated site-specific documents when they become available (e.g. updated Delegation of Responsibilities log, trial specific training logs.
- Updated Lab normal reference ranges and accreditation certificates (if required)
- Confirmation of continued capacity and capability
- Amended PIS and ICF on headed paper
- Any updates to site contact details, particularly if this affects out of hours procedures/contacts

7.12. Addition of Further Investigator Sites

- Following initial HRA/REC/MHRA approval any further Participating Sites not included in the original IRAS application must be notified to the HRA/REC as an amendment
- For CTIMPs the addition of new sites must be submitted to the HRA/REC as a substantial amendment refer to CCTU/SOP014 - Amendment Management of CTIMPS by Trial Teams. For Non CTIMPs there is no requirement to notify the MHRA
- For non-CTIMPs there is no requirement to notify the MHRA the addition of new sites is submitted as a non-substantial amendment to hra.amendments@nhs.net
- For further guidance check the HRA/IRAS websites

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

10. Associated Documents

CCTU/SOP015 Trial Master File/Site File – Essential Document Management

CCTU/SOP041 Green Light Procedure for IMP Release

CCTU/SOP047 CTIMP Set up Procedures for Trial Teams

CCTU/SOP064 Setting up International Studies

CCTU/SOP070 CCTU Led Non CTIMP Set Up Procedures

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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