Standard Operating Procedure CCTU/SOP047

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

1. Scope

This SOP describes the procedure to be followed by all trial teams running clinical trials of investigational medicinal products (CTIMPs) from funding award to trial initiation where QA and QC responsibility for regulatory oversight has been delegated or contracted to the Cambridge Clinical Trials Unit (CCTU).

2. Purpose

To ensure that trials are planned, organised and commenced in accordance with CCTU, Regulatory, Research Governance and GCP requirements.

To ensure that Investigator's 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.

Common abbreviations and definitions can be found in CCTU/INF001 Common Abbreviations and Definitions.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or jointly by CUH and UoC; or by CUH jointly with other organisations
Externally Sponsored	Sponsored by any other Trust, University or Commercial Organisation outside of the CUH remit
Sponsor	An individual , company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial
Trial Team	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
Randomisation Manager	Member of CCTU staff designated the task of randomisation

3.2. Abbreviations

Abbreviation	Meaning
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator

CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTO	Clinical Trials Officer
CTIMP	Clinical Trial of Investigational Medicinal Product
CTM	Clinical Trials Monitor
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS & ICF	Patient Information Sheet and Informed Consent Form
PV	Pharmacovigilence
R&D	Research and Development
REC	Research Ethics Committee
SSI	Site Specific Information
UoC	University of Cambridge
NIHR	National Institute for Health Research
NIHR CSP	Coordinated System for gaining NHS Permissions
CESP	Common European Submission Platform

4. Undertaken by:

Members of the Trial Team as delegated by the CI

5. Items Required

R&D/SOP001 CTIMP Delegation of Roles and Responsibilities
CCTU/SOP040 Risk Assessment Process for CTIMPs
CCTU/SOP045 Use of Vendors
CCTU/GD013 Initial MHRA Submission Guidance
CCTU/GD012 Initial HRA/REC Submission Guidance
CCTU/GD029 CTIMP Submission Checklist
CCTU/TPL001 Protocol Template
CCTU/TPL002 Patient Information Sheet and Consent Template
CCTU/TPL017 Patient Information and Consent Template 11-15 Year Olds
CCTU/TPL014 Participant ID Card Template
CCTU/TPL015 GP Letter Template

6. Summary of Significant Changes

- Change in Scope and minor change to title
- Updated to remove all sections relating to initial contact and CCTU Portfolio Adoption following the implementation of CCTU/SOP054 Initial Contact with CCTU for Setting Up Clinical Research Project Collaboration
- Changes made to items required and associated documents

- Additional information included to clarify the documentation review and pre-initiation processes
- Changes made to several sections of this document following implementation of the new HRA approval process on 31March 2016

7. Method

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

7.1. Documentation Generation

- The CTO will provide the trial team with the relevant SOPs, templates, forms and guidance documents to enable the generation of trial level documentation, including but not limited to:
  - CCTU/TPL001 Protocol Template
  - CCTU/TPL002 Patient Information Sheet and Consent Template
  - CCTU/TPL017 Patient Information and Consent Template 11-15 Year Olds
  - CCTU/TPL014 Participant ID Card Template
  - CCTU/TPL015 GP Letter Template
- All templates listed above are mandated for Cambridge Sponsored trials
- 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)
- Where appropriate, the CCTU Statistician will provide statistical information required for the protocol and IRAS application
- Where appropriate, the CCTU Randomisation Manager will provide randomisation information required for the protocol
- Where appropriate, the relevant pharmacy department should provide input into the IMP sections of the protocol, IRAS application and IMP labels
- Applications for REC, HRA and MHRA approval are generated using the on-line IRAS system (www.myresearchproject.org) and all information included in this should be correct, in a lay language and sufficiently detailed

7.2. Initial Submission Review

- Only when the Collaborative Research Letter has been signed and executed by all parties will the CTO begin the review process
- The CTIMP Submission Checklist CCTU/GD029 should be used as a guide for the documentation required by the regulatory team for review
- All submission documentation must be submitted to the CTO for review as a single package, to allow essential cross-checks to be conducted

- 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 trial team should contact any supporting departments prior to submission to the CCTU so they are prepared for any queries which may arise during the review process
- Where possible the supporting department review will be incorporated into the CCTU review timelines
- All changes required following the regulatory team review will be written, where possible, using tracked changes to allow the trial team to review and agree changes in a timely manner
- Once any agreed alterations are made, the CTO will provide the final versions to the relevant sponsor contact for final review and authorisation
- The final sponsor review will require at least two weeks to complete from the date of receipt of the final documents

7.3. Risk Assessment

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

7.4. Protocol Peer Review

- The scientific quality of the trial should be reviewed by an external expert in the field and by someone who is not involved in the trial
- The CTO will liaise with the relevant department to arrange for a suitable peer review of the protocol if not already completed by external funders charities or sponsors
    - Please note that review of the trial as part of a large programme grant does not constitute sufficient peer review of the protocol and an additional peer review would be required
- This should happen in parallel with the CCTU review of the submission documentation
- For Cambridge Sponsored Trials, CUH Trust committees include:
    - The Scientific Advisory Board (SAB)
    - The R&D Oncology Committee Meeting
    - Wolfson Research Advisory Committee (WRAC)
    - A member of the Trust's Research Advisory Committee (RAC) or by the RAC itself (both of which are organised by a member of the R&D Governance Team)
- Peer review can take up to 6 weeks to complete

7.5. Trial Supplies, Agreements & Contracts

- Refer to CCTU/SOP045 Use of Vendors
- The trial team will liaise with the pharmacy department/external sponsor to identify any IMP supply issues including importing and manufacture of IMP. This information must be provided to the CTO by the trial team

- Once a supplier has been identified, the CTO and trial team will liaise with the relevant legal team to ensure that the required agreements are negotiated and implemented (including technical agreements)
- The CTO must receive a copy of all draft agreements and any relevant site-level documents (currently Statement of Activities and Schedule of events) as part of the review process
- Where required, insurance provision must be sourced by the trial team and confirmation of provisional cover provided to the CTO
- Any 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 any trial 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

7.6. HRA/REC Submission

- The trial team is delegated the responsibility for obtaining approval from the HRA and the REC for their trial, refer to CCTU/GD012 Initial HRA/REC Submission Guidance
- The HRA/REC submission can only be made once:
    - The CTO has confirmed that the review is completed and all required changes have been made
    - A representative of the Sponsor has electronically signed the sponsor declaration page of the HRA/REC application form
    - All documents have been signed by the relevant parties
- Copies of all final signed and submitted documents must be provided to the CTO by the trial team normally within 5 working days of submission
- Copies of all correspondence with the HRA and the REC should be forwarded to the CTO in a timely manner
- Any changes required by the HRA and the REC to the submitted documents should be reviewed and agreed for re-submission by the CTO

7.7. MHRA Submission

- The MHRA submission can only be made once the CTO has confirmed that the review is completed and all required changes have been made
- The trial team is delegated the responsibility for obtaining approval from the MHRA for their trial, refer to CCTU/GD013 Initial MHRA Submission Guidance
- The final CTA Submission to the MHRA can be signed by the CI, unless otherwise stated by the Sponsor
- The CTO will facilitate the MHRA Submission via the relevant portal (currently CESP)
- Copies of all final signed and submitted documents must be provided to the CTO by the trial team normally within 5 working days of submission

- Copies of all correspondence with the MHRA should be forwarded to the CTO in a timely manner
- Any changes required by the MHRA to the submitted documents should be reviewed and agreed for re-submission by the CTO

7.8. NIHR Portfolio Adoption

- For the trial to be considered for NIHR Portfolio Adoption, the NIHR CRN Portfolio Application Form (PAF) must be generated, completed and submitted electronically in IRAS
- The PAF can be submitted at any time and does not require any signatures
- The funding award letter must be submitted with the PAF
- The trial must send confirmation to the CTO once their trial has been adopted into the NIHR Portfolio

7.9. Site-specific Submission

- Appropriate authorisation must be sought for each participating site prior to commencement of a clinical trial at a given site.
- For NHS trials where the lead R&D office and participating sites are in England, review of site-specific issues is performed by local R&D through assessing and confirming their capacity and capability to deliver the trial
  - Upon receipt of the HRA initial assessment letter, the trial team will send this letter together with the local document package to each site, including the local research team, R&D and the local CRN where relevant
  - A site specific information (SSI) form is no longer required to be submitted to a local R&D
  - Each local R&D will review the submitted documentation in accordance with local requirements within each Trust
  - Any changes requested by the local research team/R&D to the documents approved by the HRA/REC should be communicated to the CTO
  - Once all the arrangements have been put in place to provide the capacity and capability to deliver a study and HRA approval is received, participating NHS organisations should provide confirmation as outlined in the HRA approval letter
- NHS trials led from England where some participating sites are from the devolved administrations:
  - The applicant should create and transfer NHS SSI forms to local research teams for each NHS/HSC site in Northern Ireland, Scotland or Wales.
  - These should then be submitted with accompanying documents for each R&D office in accordance with the instructions from each nation.
  - For further guidance concerning NHS R&D permission in the devolved administrations please refer to: http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/

- Non-NHS trials:
  - Site-specific assessment is the responsibility of the REC, undertaking the review of the main application
  - The trial team should submit the non-NHS SSI form to the REC, together with the required documents as listed in the checklist for a non-NHS SSI form in IRAS.
  - This submission can be made in parallel with the REC submission
  - For more information refer to http://www.hra.nhs.uk/resources/applying-for-reviews/site-specific-assessment-ssa/

7.10. CRF Design, Trial Database & Randomisation System

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

7.11. HRA/REC & MHRA Approvals

- Once received, all approval documentation must be forwarded in a timely manner to the CTO for inclusion in the Sponsor file

  Please note: A requirement of REC approval is that the trial must be registered on a publicly accessible and searchable database.
  - For all phase 2, 3 and 4 CTIMPs this will be automatically included as part of the MHRA approval on the www.clinicaltrialsregister.eu website
  - 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
  - The trial team must send confirmation to the CTO once their trial is registered and available on this and any other suitable website (e.g. www.clinicaltrials.gov)

7.12. Pre Initiation

- Prior to the planned initiation meeting the CTO will provide relevant initiation documentation for completion by the trial team

- This documentation must be completed and returned to the CTO as soon as possible to allow the pre-initiation checks to be completed
- Documentation generated as part of the risk assessment mitigating action requirements must be sent to the CTO for review and confirmation in advance of the initiation meeting
- The CTO must be provided with confirmation from the CI/PI acknowledging compliance with the implementation timelines for all mitigating action requirements which are due for completion following the initiation meeting
- Only once all mitigating action documentation is agreed can the initiation meeting proceed
- The PV Coordinator will finalise and provide the trial specific PV forms (e.g. Serious Adverse Event Reporting form, CCTU FRM001, Pregnancy Reporting Form, CCTU FRM003)
- The CTM will contact the trial team and arrange trial master file, investigator site file and pharmacy file review approximately 2 weeks prior to the initiation meeting
- Any outstanding documentation for the sponsor file will be requested and must be provided prior to the meeting in order for the meeting to proceed as planned

7.13. Initiation Meeting

The initiation meeting will be conducted in accordance with CCTU/SOP024 Initiation Meeting for Sponsored CTIMPs

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. Documents are reviewed every two years

9. References

The Institute of Clinical Research, 2008, Abbreviations used in Clinical Trials.

MHRA Good Clinical Practice "Grey Guide" 2012 – 4.5 Cross-checking and quality control

10. Associated Documents

R&D/POL003 International Studies Policy

CCTU/GD015 EudraCT & IRAS Account Creation Process Guidance

CCTU/SOP024 Initiation Meetings for Sponsored CTIMPs
CCTU/SOP027 Data Management
CCTU/SOP049 Overview of Data Management Tools and Procedures

CCTU/SOP041 Green Light Procedure for IMP Release
CCTU Collaborative Research Letter
CCTU FRM001 Serious Adverse Event Reporting Form
CCTU FRM003 Pregnancy Reporting Form

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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