Standard Operating Procedure CCTU/SOP064

Setting up International Studies

1. **Scope**

This SOP is for use by study teams setting up Cambridge Sponsored studies with international participating sites, including Clinical Trials of Investigational Medicinal Products (CTIMPs).

It is applicable whether the involvement of International sites is known at study conception or added after set up.

2. **Purpose**

To ensure studies with participating sites outside of the UK are set up and managed in accordance with CCTU, Regulatory, Research Governance, GCP and country-specific requirements.

3. **Definitions and Abbreviations**

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

3.1. **Definitions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Cambridge Sponsored</td>
<td>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 &amp; Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge</td>
</tr>
<tr>
<td>CTIMPs</td>
<td>Clinical Trials of Investigational Medicinal Products <strong>Please note, a study not considered as a CTIMP in the United Kingdom could be considered as a CTIMP under the legislation of another country and vice versa.</strong></td>
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<tr>
<td>Funder</td>
<td>Commercial organisations, governmental bodies or charities providing funding and support, e.g. Investigational Medicinal Product, to carry out research</td>
</tr>
<tr>
<td>International site</td>
<td>A lead or participating site located outside of the UK</td>
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<tr>
<td>Lead (non-UK) site</td>
<td>A participating site in a country that will have additional responsibilities over the other participating sites in the country, such as: obtaining Regulatory Authority approval, IRB/IEC opinion on-going maintenance of the approvals</td>
</tr>
<tr>
<td>Local Sponsor</td>
<td>A party responsible for the finance, conduct and management, in accordance to local regulations, of the study to be run in</td>
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parallel with the Cambridge Sponsored study

Country Code
ISO Alpha-2or3

The ISO country codes are internationally recognised codes that designate every country and most of the dependent areas a two-letter combination or a three-letter combination that stands for a country or a state. The three letter code can also be used at events/functions with attendees from various countries.

Personal data

Any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. This could include pseudo anonymised data – e.g. key-coded.

### 3.2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>CA</td>
<td>Competent Authority (could also be known as Regulatory Authority)</td>
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<tr>
<td>CCTU</td>
<td>Cambridge Clinical Trials Unit</td>
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<tr>
<td>CTC</td>
<td>Clinical Trial Coordinator</td>
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<td>CUH</td>
<td>Cambridge University Hospitals NHS Foundation Trust</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>ICH GCP</td>
<td>International Council for Harmonisation Good Clinical Practice</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>SADEs</td>
<td>Serious Adverse Device Events</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>UoC</td>
<td>University of Cambridge</td>
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</table>

### 4. Undertaken by

Members of the Coordinating Team as delegated by the CI
Members of the CCTU as delegated by the Sponsor

### 5. Items Required

- R&D/POL003 Trust Sponsored International Studies
- R&D/SOP011 Safety Reporting for Medical Device Trials
- CCTU/FRM021 Risk Assessment Form for CTIMPs
- CCTU/SOP011 Monitoring Trust Sponsored CTIMPs
- CCTU/SOP014 Amendment Management of CTIMPs by Study Team
- CCTU/SOP016 Packaging Requirements for the Transport of Biological Samples
- CCTU/SOP019 Urgent Safety Measures and Temporary Halt for CTIMPs
- CCTU/SOP024 Initiation Meeting for CTIMPs
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. **Sponsor Agreement in Principle and Research Board Approval**

In accordance with R&D/POL003 Sponsor Agreement in Principle is obtained on a study by study basis as part of the feasibility process.

The Cambridge Sponsor may choose to proceed with a local Sponsor in the participating country/countries. The decision must be confirmed in writing by the Research Board.

Formal, written Research Board Approval is required for all international countries/sites on a per study basis prior to the commencement of any formal set-up activities.

7.2. **Country-Level Feasibility**

The coordinating team should complete a feasibility questionnaire for each country using CCTU/TPL078 International CTIMP/Study Country-Level feasibility Questionnaire and provide the completed form to the R&D legal team for discussion with the Cambridge Sponsor.

The information gathered from the feasibility questionnaire should be used to plan study/country set up.

7.3. **Funding**

At the point of grant application the additional costs of setting up an international participating site must be taken into consideration e.g.

- IEC and CA reviews require payment in some countries; this is expected to be covered by the trial grant
- The Cambridge Sponsor will not cover these costs under any circumstance
• Costs for professional translation services
• Insurance costs; some countries carry a heavy insurance cost
• Monitoring activities should be considered and budgeted for accordingly
• Some funders will not cover all costs (some charities will not cover the cost of insurance), therefore alternative arrangements must be made to cover these costs separately

7.4. Protocol Design

7.4.1. Participant Population

• The funder may set specific limits on the involvement of participating countries including the number of participants recruited internationally. This will be included in the funding agreement
• In studies that include vulnerable populations, such as children/young people and adults lacking capacity, local governing legislation must be taken into account
• Potential differences e.g. standard of care, cultural practice and standards of literacy should also be considered when designing the protocol and participant documents

For Paediatric research,
• The legal age of children and reporting requirements differ in each country this must be taken into consideration when planning data cleaning and reporting activities. For example within a trial setting, Japan considers adults to be persons aged 21 or over, the UK is 16.

7.4.2. Data Collection, Data Protection and Data Transfer

• The difference in definition of personal data and its governing legislation in different countries must be considered in the protocol design
• Participant Information Sheets should include a statement noting, if applicable data may be sent to another country with a lower level of data protection
• When designing data capture tools, i.e. Case report forms the accessibility and language used must be considered
• The transfer of data must be set up in a secure manner refer to CCTU/SOP029 Data Transfer. Access must be restricted to members of coordinating team
• Where there is a Local Sponsor following the same protocol with a data transfer agreement in place, data collected can be processed by the coordinating team.

7.5. Set up in Each Country

• A lead site should be selected for each country and contracted to perform the additional responsibilities such as acting as the main point of contact for that country. This will usually include additional payments
• The coordinating team can retain the responsibility if this is not an option, however this must be agreed by the Sponsor in advance
• The coordinating team is required to perform a feasibility assessment of each international site to assess their suitability, experience and available resources (facility, staffing and patient population) to determine the likelihood that the site can:
  ▪ Open within reasonable timelines
  ▪ Meet the recruitment target
  ▪ Perform the trial in accordance with protocol and GCP regulations
• In certain circumstances it may be appropriate for the local lead site to perform the feasibility assessment of potential sites within their jurisdiction on behalf of the Cambridge Sponsor
• The outcome of the feasibility assessment should be used to determine the priority for opening sites, due to the additional resources required to open an international site

7.6. Agreements

• The CUH (and UoC if jointly sponsored) legal team will lead the preparation and negotiation of the required agreements
• In addition to a contract (or equivalent) between the Sponsor and the Funder and/or the participating site agreement between the Sponsor and participating sites, there will be:

  A lead site agreement
  This must clearly detail the delegation of responsibilities between the Sponsor and the selected lead site in each country. The lead site will normally be delegated responsibilities to:
  ▪ Obtain country-level approvals, including amendments
  ▪ Maintain a country level TMF and site-information file for the sites within the country
  ▪ Fulfil local safety reporting requirements to relevant regulatory authority and ethics committee
  ▪ Fulfil local serious breach and urgent safety measure reporting to the relevant regulatory authority and ethics committee
  ▪ Carry out monitoring activities as directed by the monitoring plan including close-out activities and preparation for archiving

• Depending on the design of the study, other agreements may be required.
• Where there is a Local Sponsor, a collaboration agreement (and data exchange agreement if required) will be set up.

7.6.1. Indemnity / Insurance

• The cost for insurance will not be covered by the Cambridge Sponsor under any circumstances
• Local indemnity cover for each participating country (which may include non-negligent harm) must be identified. If this is not an available option, each site must arrange their insurance cover for the entire duration of the study
• Where a study is jointly sponsored with University of Cambridge, additional protocol design insurance cover for the entire duration of the study will be required for the relevant aspects of the international study
- This is arranged by the UoC insurance office and it is country specific (countries considered high risk in terms of clinical study conduct will have higher insurance premiums)
- Maintenance of insurance cover includes but is not limited to:
  - Ensuring renewal arrangements are in place to avoid cover lapsing
  - Ensuring the insurance provider is informed of amendments where applicable
  - Providing a valid insurance policy and certificate of insurance to R&D legal for review
- Where there is a Local Sponsor, it will be the local Sponsor’s responsibility to arrange local indemnity/insurance cover for the duration of the study.

### 7.6.2. ICH GCP

- For CTIMPs, the principles of GCP in accordance with the country’s legislative requirement should be followed
- For CTIMPs where study data is to be used as part of a licensing application for marketing authorisation, it is a legal requirement to follow the International Council for Harmonisation Good Clinical Practice (ICH GCP)
- Essential documents that make reference to specific guidelines should be adapted to refer to this
- For non-CTIMPs, the local requirements for GCP training should be followed

### 7.6.3. Collection and Movement of Samples

- A Material Transfer Agreement will be required for the collection and movement of all samples if it has not already been incorporated in a Participating Site Agreement
- Where the collection of biological samples is an outcome measure, each country’s regulations and requirements regarding the import/export of biological samples will need to be considered as part of the feasibility assessment. Note: some countries prohibit exporting biological samples, others, such as China, can be difficult and require special export permits
- CCTU/SOP016 and 044 detail some minimal considerations for the management of samples. In addition consider the following:
  - The time and cost to transport samples, including returns if applicable
  - The transport conditions to preserve integrity
  - Temperature monitoring during transport if applicable
  - Identification of samples (site identifiers must be applied to all samples)
- Where there is a Local Sponsor following the same protocol and where a material transfer agreement is in place samples collected can be processed by the coordinating team.

### 7.7. Risk Assessments

A risk assessment will be performed by the R&D legal team for each participating country with recommendations for risk management measures. These should be incorporated into risk assessment activities below:
For CTIMPs
- The CCTU Regulatory team will perform a Sponsor risk assessment to identify risk mitigating actions according to CCTU/SOP040

For non-CTIMPs / Device Studies
- It is highly recommended that a risk assessment is carried out following CCTU/SOP040 using CCTU/FRM021 appropriately adapted by the allocated Clinical Trial Coordinator overseen by appropriate team lead
- Risk mitigating actions identified must be:
  - Satisfactorily addressed by the study team within the specified timeline
  - Reviewed routinely to ensure timely completion (for example, included as part of Study Management Group/Team meeting agenda)

7.8. Essential Document Management
- Where the study is Cambridge-Sponsored, the following essential document management hierarchy should be followed unless otherwise stated in the relevant agreements:

<table>
<thead>
<tr>
<th></th>
<th>Trial Master File (CCTU/TPL032)</th>
<th>Country -Level TMF (CCTU/TPL076)</th>
<th>Site File Information (CCTU/TPL034)</th>
<th>Investigator Site File (CCTU/TPL033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordinating team</td>
<td>X* *(TPL077)</td>
<td>X – UK sites only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead site at each country</td>
<td>X</td>
<td>X – ALL sites within the Lead site’s country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participating Site</td>
<td></td>
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<td>X</td>
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* Green light procedure/ Lead site initiation documents for each participating country, including subsequent amendments, must be maintained within the TMF using TPL077 International TMF Country Level Essential Documents.

**Where there is a Local Sponsor**
- The local Sponsor will set up their own Trial Master File (CCTU/TMF034)
- The Coordinating team maintain a file to document activities and correspondence with the local Sponsor

7.8.1. Local Adaptation of Documents / Version Control
- Global documents generated by the coordinating team will require local adaptation in order to meet local governing legislation
- The document should be identified with a country code as part of version control
- Local adaptation may include additional wording required to satisfy local requirements in relation to data controls, insurance and regulatory/legal processes. It will be necessary to provide these to the R&D Legal team for review as per R&D/POL003
Every country has its own templates for REC submission and PIS. The local study team will be responsible for their completion and submission.

Where there is a Local Sponsor, depending on the number of countries involved, the language and other considerations, it is possible that local adaptation can be included as part of the main protocol. This should be in consultation with the local Sponsor contact.

7.8.2. Documents that Require Translation

Whilst the Sponsor does not specify that translation activities must carried out by a certified/commercial translator, the coordinating team and the lead site must ensure that translations are carried out by persons with an appropriate understanding of clinical studies and medical terminology.

Documents that require translation include: Participant Information Sheets, Informed consent forms, Participant ID card, advertisements, letters to participants, IMP labels, patient facing CRFs/questionnaires etc.

The translated document must be back-translated and checked for accuracy.

The R&D legal team must review the back-translated documents specifically for legal terms and insurance/indemnity provision.

Care should be taken when translating data collection documents in studies where data entry is performed centrally in another country. English prompts should remain on the document to aid data entry.

Where there is a local Sponsor, the local Sponsor is responsible for the translation of documents.

7.9. Investigational Medicinal Products / Medical Device Considerations

IMP

The marketing status of an IMP differs across countries this will need to be taken into consideration when determining requirements for:

- Importing
- Labelling
- Release

In some cases, IMP may be provided by a separate company in different countries.

Based on the above, additional agreements may be required if:

- There is a local Sponsor
- There are separate arrangements for the provision of IMP with the manufacturer at the International sites.

Medical Device

The device used in a device study must be:

- Labelled appropriately in accordance to local regulatory requirements
- Procured, distributed, calibrated, maintained, serviced throughout the duration of the study and all records maintained
7.10. Amendments

- Refer to CCTU/SOP014 Amendment Management of CTIMPs by Study Teams
- Once the Cambridge Sponsor has given the authorisation to proceed with an amendment, it is the coordinating team’s responsibility to:
  - Distribute the amendment documents to the lead site for local adaptation
  - Submit to their local authority in a timely manner, usually within 10 working days to enable the implementation of the new amendment across the participating countries in a similar timeframe
- Upon receipt of the relevant approvals it is the lead site’s responsibility to:
  - Forward the approval documents to the coordinating team and participating sites
  - Ensure institutional approval is obtained by each participating site in their country according to local requirements
- Where there is a Local Sponsor, once the Cambridge Sponsor has given authorisation to proceed, the coordinating team will provide the documents to the local Sponsor for submission and implementation.

7.11. Pharmacovigilance Reporting / Safety Reporting Requirements / Regulatory Reporting Requirement Time Lines

- All Investigators must report Serious Adverse Events / Serious Adverse Reactions / Suspected Unexpected Serious Adverse Reactions to the Cambridge Sponsor in accordance with the protocol
- The lead site is responsible for notifying the regulatory authority and ethics committee of reportable events in accordance to local reporting requirements
- The coordinating team and lead site must work cooperatively to prepare and submit safety reports according to local requirements
- The following should be considered:
  - Reference Safety Information (RSI) may be different as a result of IMP consideration noted in section 7.8, as such, this could have an impact on:
    - SUSAR reporting
    - Line listings
  - Reporting requirements differ in different countries.
  - In the UK, the MHRA requires all “UK-relevant SUSARs” to be reported, the agency’s definition of “UK-relevant” includes:
    - SUSARs originating in the UK
    - SUSARs originating outside the UK where the sponsor has an ongoing study in the UK involving the same medicinal product

Medical device studies
- Serious Adverse Device Effects (SADEs) and other safety events involving a medical device undergoing clinical investigation should be reported according to local regulatory requirements, refer to R&D/SOP011 Safety Reporting for Medical Device Studies.
7.11.1. Urgent Safety Measures

- Refer to CCTU/SOP019 Urgent Safety Measures and Temporary Halt for CTIMPs for guidance
- All investigators must identify and implement Urgent Safety Measures (may be known differently in other countries). Once an Urgent Safety Measure has been implemented the Investigator must inform the Chief Investigator within the same working day or no later than 24 hours from its implementation. The CI must then follow CCTU/SOP019 to notify the MHRA, REC, Sponsor and other investigators
- The lead site must then notify their regulatory authority and ethics committee accordingly, including any subsequent amendment(s) identified as a result of the urgent safety measure

7.12. Setting up International Sites

7.12.1. Lead Site Initiation and Regulatory Green Light

- Refer to CCTU/SOP024 Initiation Meeting for CTIMPs
- The Cambridge Sponsor initiation must take place at the Sponsor site before the lead site initiation can take place
- Lead site initiation must take place before initiation of other sites in the country
- The lead site initiation can only take place after the coordinating team are satisfied that the site has obtained all regulatory, ethics and institutional approval and have completed the set up activities

CTIMPs

- The Lead Site Initiation checklist (CCTU/TPL075) must be completed and provided to the CCTU prior to the initiation meeting as part of green light procedure referred to in R&D/POL003

Other studies

- The CTC must complete The Lead Site Initiation Checklist (CCTU/TPL075) and be satisfied that all the required documents are in place prior to performing the initiation meeting
- Participating sites in a country must not be initiated until the lead site has been initiated and the set up activities are near completion (Refer to CCTU/FRM064 Participating Site Initiation Checklist). The initiation meeting can be led by the coordinating team but may be delegated to the lead site if it has been agreed in the lead site agreement. Initiation of international sites and training to study-specific activities can take place by teleconference

7.12.2. Monitoring / Sponsor Oversight of International Sites

Monitoring activities at international sites will be included in the Monitoring Plan
- The frequency and the type of monitoring activities will be agreed with the Cambridge Sponsor and coordinating team
- All international sites are expected as a minimum to participate in remote monitoring. An on-site visit whether routine or triggered will be delegated to the lead site
• Close out visits can be performed remotely or on-site. Close-out activities will be facilitated by the local lead site

**CTIMPs**

• The monitoring plan will be generated by the allocated CCTU Monitor in accordance to CCTU/SOP011 Monitoring Trust Sponsored CTIMPs

### 7.13. Vendors

• The coordinating team must inform the Cambridge Sponsor if any aspect of the study is contracted out to a vendor
• A participating site is not expected to outsource study related activities to a vendor; however if a vendor is required, the Cambridge Sponsor must be informed in advance

Where there is a Local Sponsor, they must inform the Cambridge Sponsor in advance of appointment of the vendor. The Sponsor will require assurance from the Local Sponsor on the suitability and qualification of the vendor to perform the delegated clinical trial/study related activities.

#### 7.13.1. Cambridge Sponsored CTIMPs with a Local Sponsor

• For studies where the Cambridge Sponsor has contracted the running of the study in a particular country or region to a local sponsor the following also should also be noted:
• The local Sponsor assumes all legal responsibilities according to local regulations in relation to:
  - Obtaining CA/RA approval before recruitment commences
  - Obtaining IEC approval before recruitment commences
  - Obtaining and maintaining IRB approval for their own site
  - Reporting Urgent Safety Measures (where applicable)
  - Fulfilling safety and annual reporting requirements to CA and IEC
  - Fulfilling End of trial reporting requirements
  - Implementation of a Quality Management System, including monitoring
  - Retention of study documents
  - Site management responsibilities if multi-centre, including participating site agreements, IRB approval
  - For CTIMPs, ensure IMP provision is arranged and the IMP is labelled in the local language and in accordance to local requirements
• The Cambridge Sponsor must ensure:
  - The communication/escalation pathway is established with the local Sponsor
  - Access to data is possible for monitoring/audit purpose
  - They have the right to audit compliance with the collaboration agreement see 7.6
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
    CCTU/SOP045 Use of Vendors

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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<thead>
<tr>
<th>Review date</th>
<th>2 years (or earlier in light of new evidence) from approval date</th>
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<td>CCTU QA</td>
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