1. **Scope**

This SOP covers all Cambridge-sponsored CTIMPs that fall under the UK Clinical Trials Regulations.

This document should be read with CCTU/SOP047 CTIMP Start-up/Set up Procedure for Trial Teams or CCTU/SOP048 CTIMP Start-up/Set up Procedures for the Regulatory Team as appropriate.

2. **Purpose**

Article 43 of Annex 13 requires that investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step release procedure: certification by the Qualified Person, termed as ‘technical release’ and release following fulfilment of the requirements of EU regulations, termed as ‘regulatory release’. The purpose of this SOP is to:

- Describe the two-step IMP release process
- Provide guidance on how to ensure that the two-step process is implemented in compliance with the UK clinical trials regulations
- Clarify when IMP is hospital stock a technical release is not always required

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>
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<tr>
<td>Batch</td>
<td>A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous. In blinded studies the batch numbers of the IMP and the matching nIMP or placebo are usually identical to maintain the blinding to the site staff at the point of dispensing.</td>
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<tr>
<td>Sponsor</td>
<td>An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.</td>
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3.2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>CCTU</td>
<td>Cambridge Clinical Trials Unit</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
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<td>CTIMP</td>
<td>Clinical Trial of Investigational Medicinal Product</td>
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<td>EU</td>
<td>European Union</td>
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<td>GTAC</td>
<td>Gene Therapy Advisory Committee</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>MIAIMP</td>
<td>Manufacturer’s Authorisation for Investigational Medicinal Product</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>QP</td>
<td>Qualified Person</td>
</tr>
<tr>
<td>R &amp; D</td>
<td>Research and Development</td>
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<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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4. Undertaken by

This SOP applies to staff involved in Cambridge-Sponsored CTIMPs.

5. Items Required

CCTU/SOP047 CTIMP Set-Up Procedure for Trial Teams
CCTU/SOP048 CTIMP Set-Up Procedures for the Regulatory Team

6. Summary of Significant Changes

Update to the definition of Batch
Clarification of Sponsorship
Addition of HRA approval
Update reference information to GCP (R2)
Clarify when the IMP is hospital stock a technical release is not always required

7. Method

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

7.1. The Two-step IMP release

Step One
- The QP batch certification is the first of the two-step release process
- This is applicable when an MIA (IMP) is required, i.e., a manufacturer and/or importer is listed on the Clinical Trial Application for certification of finished IMP or placebo
Step Two

- The regulatory green light is applicable to all CTIMPs.
- Further guidance should be sought from the Sponsor in cases where the IMP will be sent direct from the IMP supplier or manufacturer to the patient without the involvement of Pharmacy

7.1.1. QP Batch Certification

- This is the certification by a QP, as defined in the regulations, before a finished IMP batch is released for use within a clinical trial, confirming that the requirements of Article 13(3) of Directive 2001/20/EC have been met
- The QP has a legal responsibility as defined in Article 13(3) above, to ensure that the IMP has been manufactured in accordance with EU GMP and meets the conditions of the product specification files (PSF), IMP dossier and clinical trial authorisation (CTA)
- A prerequisite of QP batch certification is receipt of the full Clinical Trial Application, IMP cannot be authorised for distribution prior to the CTA being granted
- The QP certification must be provided by a QP named on the MIA (IMP) licence specified in the Clinical Trial Application as responsible for the manufacturing and/or importation of the finished IMP
- The QP certification statement is the final release of the batch. Confirmation must be sought that TSE statements are part of the QP certification process if not explicitly listed on the certificate
- Certification is issued for each batch produced and must be retained by the sponsor – or delegate for review by the MHRA until the end of the trial archiving period
- Additionally to QP certification, if an IMP is manufactured outside the EEA, a QP declaration of equivalence to EU GMP is required for each IMP that is listed in the Clinical Trial Application
- For multicentre Cambridge-sponsored CTIMPs, it is the sponsor’s responsibility to hold the QP certification documents, and to have a system to track IMP to site on a batch-specific basis to enable management of expired stock and recall if required. QP batch certificates may be supplied to other participating sites, either by design or upon request, unless this would compromise the blinding of a trial in which case an explanatory file note should be issued

7.1.2. Regulatory release and authorisation to start the trial

- This is the second of the two-step process and is carried out at both the Sponsor site and at participating sites; however it must always be carried out at the CUH site before other participating sites
- Regulatory Green Light at CUH is carried out by the Sponsor, for participating sites it is delegated by the Sponsor to the CI as detailed in CCTU/SOP039
- Once QP batch certification has occurred, the sponsor will then authorise the commencement of the clinical trial as long as the provisions of the EU directive have been met. They are:
  - Favourable opinion from the REC
Approval by the HRA
Notice of acceptance from the MHRA
Favourable opinion from the GTAC (only applicable to clinical trials using somatic cell therapies)
The Sponsor is legally responsible for ensuring that both steps are completed prior to the release of IMPs for use in a clinical trial
REC (or GTAC) and MHRA approvals must be in place before the IMP can be released for use at participating sites
If any IMP is received at the participating sites before full sponsor approval it should either be quarantined or returned to the supplier (at the discretion of the sponsor) until all the required approvals are in place

Sponsor Site (CUH) release process
- A trial initiation meeting at CUH will take place as described in CCTU/SOP047 or CCTU/SOP048 as appropriate after which the Capacity and Capability confirmation letter will be issued to the trial team
- The Capacity and Capability confirmation letter officially signals the Sponsor site’s approval for the trial to commence at the Sponsor site. After this, the trial team can then request IMP release at the CUH site
- When the IMP is received by the CUH Clinical Trials pharmacy, checks will be completed according to pharmacy SOP/CT013. This is to ensure that the batch of IMP supplied corresponds with the details on the delivery documents and the contents of the CTA
- If the checks are satisfactory, the Clinical Trials pharmacist will complete a release checklist and approve the IMP for use at the CUH site ie. Local green light only, according to pharmacy SOP CT001

IMP release at participating sites
- The mandate for IMP release to other participating sites is delegated to the Chief Investigator (CI) and the trial co-ordinating centre
- The CI and/or the trial co-ordinator will conduct a local initiation either onsite at the participating sites or remotely. After this has occurred and the local Capacity and Capability letter has been issued, authorisation is given for IMP to supplied (Refer to CCTU/SOP039)

7.2. Additional or New IMP batches & Changes to Manufacturer details on the CTA
- Additional or new batches of IMP will undergo QP batch certification as described in sections 7.1.1
- If the REC, HRA, MHRA, Sponsor and Capacity and Capability are still valid, IMP may continue to be issued to sites
- If the REC, MHRA, HRA, Sponsor and Capacity and Capability approvals have been withdrawn because of Protocol or Regulatory non-compliance, they must be re-instated before the IMP is released for use at the affected sites
- Any changes made to the manufacturer or supplier’s details such that they alter the initial contents of the CTA would result in a substantial amendment. Follow CCTU/SOP014 Amendment Management of CTIMPs by
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"
The Medicines for Human Use (Clinical Trial) Regulations 2004 (SI 2004 No. 1031) as amended
MHRA Rules and Guidance for Pharmaceutical Manufacturers & Distributors ("Orange Guide")
ICH Guideline for Good Clinical Practice, E6 (R2)

10. Associated Documents
CCTU/SOP039 Setting up and Opening a Participating Site for Cambridge Sponsored Trials
CCTU/SOP014 Amendment Management of CTIMPs by Trial Teams
CCTU/SOP020 Amendment Management of CTIMP by the Regulatory Team
SOP/CT013 Clinical Trials: Receipt of Medication
SOP/CT001 Clinical Trials: Investigational Medicinal Product Management and Pharmacy Set-Up Procedure

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.

<table>
<thead>
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<th>2 years (or earlier in light of new evidence) from approval date</th>
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<tr>
<td>Owning department:</td>
<td>CCTU QA</td>
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<tr>
<td>Supersedes:</td>
<td>CCTU/SOP041 V3</td>
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<tr>
<td>Local reference:</td>
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