University of Hertfordshire

IMP MANAGEMENT FOR UH SPONSORED AND CTSN SUPPORTED CLINICAL STUDIES

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for IMP management at the University of Hertfordshire

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Version Number: 1.0	**Review Date:** 2 - 3 years (or as required)

1. BACKGROUND

Section 5.12, 5.13 and 5.14 of The International Conference on Harmonisation of Good Clinical Practice (ICH GCP) describes the information, manufacturing, and packaging, labelling, coding, supplying and handling of IMP.

Part 6 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument: 1031) details the regulations surrounding the manufacture and importation of IMPs. The regulations require that IMPs used in clinical trials (CTIMPs) are manufactured to Good Manufacturing Practice (GMP) standards and that GCP is adhered to.

This SOP will focus on IMP activities that the University of Hertfordshire (UH) may undertake as sponsor of a clinical trial or that the Clinical Trials Support Network (CTSN) may support and as such, will not be an exhaustive operating procedure on all aspects concerning IMPs in clinical trials.

UH CTSN is not currently involved in the manufacture or packaging of IMPs. This will be the responsibility of the pharmaceutical company (or other external company) involved in the clinical trial, either as funder or provider of the IMP and should be adequately detailed in all technical agreements. The pharmaceutical company (or other external company) is responsible for conducting final checks before release of IMP to the research site. This should be done by the Qualified Person (QP) to ensure that each batch has been manufactured to GMP and all checks are in place before dispatch.

This SOP will not cover dispensing of IMPs as this will be under the remit of the pharmacy departments in each host organisation (e.g., NHS Trust) involved in the trial.

2. PURPOSE

This SOP describes the Investigational Medicinal Product (IMP) management processes that the CTSN complete for Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by UH or supported by the CTSN.

The SOP outlines the CTSN's responsibilities in ensuring that the provision of IMP in UH sponsored/CTSN supported studies is compliant with GCP, GMP and Good Distribution Practice (GDP) guidelines.

3. APPLICABLE TO

This SOP applies to Medicines and Healthcare products Regulatory Agency (MHRA) regulated UH sponsored or CTSN supported studies only.

4. RESPONSIBILITIES

This SOP must be followed by the Chief Investigator (CI), Principal Investigator (PI), Trial Pharmacy Lead, monitors and other team members involved in the management of IMP.

The details of who is responsible for the various aspects of IMP management should be detailed in the delegation of responsibilities table in the sponsorship agreement and any additional technical agreements or contracts.

It is the responsibility of the Sponsor to have procedures in place to ensure that the manufacturing, packaging, labelling, releasing, and distributing of the IMP is conducted according to the principles of GMP and Good Clinical Practice (GCP), delegating specific responsibilities accordingly.

It is the responsibility of the Head of the CTSN to ensure that this SOP is updated by the review date or as necessary.

5. PROCEDURES

5.1. Management/supply of IMP

The CI, with instructions from the relevant pharmaceutical company and in collaboration with the Trial Pharmacy Lead, should determine acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, for all IMPs in the trial. The CI should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations. IMPs should be stored in the pharmacy department, under the supervision of trained qualified pharmacists. In certain circumstances, it may be necessary to store IMP outside of Pharmacy to allow expedited or out of hours access. This provision will be

discussed with the PI, Pharmacist and IMP supplier, where appropriate. An out of Pharmacy storage assessment will be performed by a qualified Pharmacist to ensure that the storage space meets the required standards and appropriate monitoring is in place.

The CI should ensure that written procedures are provided to the local sites involved in the clinical trial include instructions for the handling and storage of IMP(s) and include robust documentation. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused IMP(s) to the CI (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement(s)).

For IMPs used within their Marketing Authorisation (MA), an up-to-date summary of product characteristics (SmPC) which is used as part of Reference Safety Information (RSI) must be included in the Trial Master File (TMF) and provided to the Trial Pharmacy Lead. The CI is responsible for ensuring the SmPC is reviewed in a timely manner or at least annually and any change should be notified to the Trial Pharmacy Lead and an updated SmPC added to the TMF. Current SmPCs can be accessed at http://www.medicines.org.uk/.

For unlicensed IMPs an Investigators Brochure (IB) which is used as part of the RSI must be included in the TMF and provided to the Trial Pharmacy Lead from the manufacturer.

The CI is responsible for ensuring the Investigational Medicinal Product Dossier(IMPD) /Simplified IMPD (sIMPD)/IB is reviewed in a timely manner or at least annually and any change should be notified to the clinical trial pharmacist and the updated document added to the TMF.

If there is a placebo, the sponsor will provide guidance as to whether a sIMPD or IMPD is required.
It is the responsibility of the CI to ensure that SmPC/IMPD/sIMPD/IB updates are checked regularly and any significant safety/quality changes must be submitted as substantial amendment to the regulatory bodies.

5.2. Coordination with Trial Pharmacy Lead

The Trial Pharmacy Lead should be involved early in the set-up of the clinical trial.

Information regarding the trial that should be discussed with the Trial Pharmacy Lead includes (but is not limited to):

- Purpose of the study.
- Explanation of the responsibilities of the various parties involved.
- Codes, e.g., for patient randomisation or unblinding.
- Numbers and recruitment parameters of patients as trial participants.
- Description of the IMP and any relevant handling/Control of Substances Hazardous to Health (COSHH) data.

- Identification of all IMPs and Non-Investigational Medicinal Product (NIMPs).
- IMP sourcing.
- IMP manufacturing/packaging plan(s).
- Calculation of overall IMP requirements for the study.
- IMP distribution plan.
- IMP blinding processes (if applicable).
- IMP labelling.
- IMP costing/funding arrangements.
- Interactive Web Response System (IWRS) systems (if applicable).
- Vendor assessment (if applicable).
- IMP out of pharmacy storage assessment (if applicable).

5.3. Coordination with contracts team

All IMP trials where IMP is manufactured by a third party or supplied by third party, there should be a technical agreement or equivalent in place. The contracts team should be involved early and discuss the project to initiate the set-up of the clinical trial.

The Trial Pharmacy Lead should review the relevant sections of contracts and technical appendices to ensure they accurately describe IMP management arrangements prior to execution.

Subsequent amendments to contract should also be reviewed by the Trial Pharmacy Lead if they affect IMP management.

5.4. IMP Documentation: IMP management plan, pharmacy manual, Clinical Trial (CT) prescription and accountability logs

Use the template IMP Management Plan and pharmacy manual to detail the IMP management procedures for the study.

The IMP management plan describes overall IMP management by the CI and coordinating team, while the pharmacy manual describes site-level procedures. For single-centre trials, the pharmacy manual and IMP management plan can be combined into a single document.

Clinical Trial prescriptions should be developed unless the study protocol and risk assessment explicitly state that study specific prescriptions will not be used. The prescription template should include details of any protocol dose alterations, escalations and treatment breaks to prompt the study team to prescribe correctly.

These documents must be finalised before the study begins.

5.5. Distribution

It is the sponsor's responsibility to ensure that IMP is supplied, packaged, labelled and released in accordance with the regulations. A manufacturer or

distribution company may carry out shipments of trial supplies to sites on behalf of the Sponsor.

IMPs should remain under the control of the manufacturer until the certification by the QP (technical release) and authorisation to the CI (regulatory checks complete) have been completed fulfilling the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC.

A detailed record of shipments made by the manufacturer or importer should be maintained. It should particularly mention to whom the shipment is addressed and delivered.

Once an IMP has been delivered to a site, it should not subsequently be transferred to another site, without first being returned to the manufacturer or distribution company for inspection and further QP release. The IMP would then be available for delivery to another site. Documentation (quantity, locations, dates, method of transfer) on the IMP transferred should be maintained.

Transfer of stock within a pharmacy department in a same trust hospital is not considered as site-to-site transfer.

5.6. Receipt

Checks should be carried out by site pharmacy staff upon receipt of IMP and would typically include:

- Ensuring supplies are correctly addressed.
- Ensuring all packaging is intact.
- Ensuring that the quantity, batch/serial numbers, correspond with shipment form.

5.7. Accountability

IMP accountability logs should be kept for all CTIMPs. See the appendices for a template log.
These logs should detail at least:

- Trial Identifiers e.g., Trial Name, EudraCT number, PI Name, Institution and IMP name.
- Participant identification code.
- Date dispensed.
- Visit number – if applicable.
- Dose.
- Kit number - if applicable.
- Quantity dispensed.
- Batch number.
- Expiry.
- Date returned (if applicable).
- Quantity returned.
- Recorder’s initials.

All IMPs should be stored and dispensed by the hospital pharmacy at site and managed to the same standards as licensed medicines. IMPs must not be stored in offices, clinics or ward areas unless by prior written agreement with pharmacy.

Some pharmacies maintain their drug accountability databases and local practice should be utilised as much as possible so long as it meets legal requirement.

Pharmacies can use their own log if they meet the minimum requirement mentioned above.

5.8. Labelling

This section discusses the labelling requirements for IMPs used in clinical trials which come under the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004.

An example label should be included with the application for Clinical Trials Authorisation (CTA) to the MHRA.

5.8.1. IMP used within its marketing authorisation

For IMPs used within its marketing authorisation (MA), the product can be labelled in accordance with the requirements for a dispensed medicine (Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994).

However, for consistency with other countries, UH CTSN recommends that IMPs are labelled following the guidance of GMP Annex 13 (appendix 1).

Thus, it would be appropriate to add an additional label with the following information:

i. The name of the investigator.
ii. Trial specific code, e.g. EudraCT number.
iii. Code for the trial participant.
iv. For Clinical Trial Use only.
v. The cautionary label “Keep out the reach of children” is a legal requirement on all UK dispensed medicines.

The quantity of dosage forms (tablets, capsules etc) is generally also added for dispensed medication.

5.8.2. IMP used outside its marketing authorisation

Guidance on the requirements of IMPs used outside their MA is given in Annex 13 of the European Union’s Good Manufacturing Practice (GMP) documentation.

5.8.3. Labelling in placebo/blinded trials

In placebo-controlled trials or blinded trials, it would be necessary to present all supplies in consistent packaging with consistent labelling to maintain

blinding. If the original product's MA holder is prepared to provide packs of the matching placebo, the company may agree to provide them in similar containers and with consistent labelling with the IMP. In other circumstances, consistency is likely to be best achieved through repackaging and full labelling.

In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency but does not permit undetectable breaks of the blinding.

All trials including double blinded trials are dispensed by pharmacy using trial specific dispensing procedure.

5.9. Return or destruction of IMP

At the end of the trial overall reconciliation of supplies must take place. Any discrepancies should be reported to the Sponsor. Trial supplies should be returned as specified in written procedures approved by the sponsor. Returned supplies should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned supplies should be kept. Supplies will not be destroyed without approval from the sponsor.

Drug destruction should be discussed with the pharmaceutical company and the pharmacy department to determine how the process will be undertaken and agreed by the sponsor.

Documented evidence of destruction should be recorded on a destruction log and filed in the site file.

5.9.1. Recalls

The sponsor should maintain a system for retrieving IMP and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion expired product reclaim).

Procedures for retrieving trial supplies and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator needs to understand their obligations under the retrieval procedure. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a trial has a system for communicating to the trial team the need to recall any product supplied.

Site staff should be trained in the IMP recall procedure.

5.10. Incident Reporting

Incidents that occur as part of the trial should be documented as protocol deviations and/or protocol violations and submitted to the sponsor.

6. RELATED DOCUMENTS

IMP Management Plan Template
Pharmacy Manual Template
Accountability Log Template
Destruction Log Template

7. APPENDICES

Appendix 1: Annex 13 labelling requirements for CTIMPs

8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change

9. AUTHORSHIP & APPROVAL

Author Claire Rourke

Signature  **Date** 9th March 2022

Pro-Vice Chancellor (Research and Enterprise) Approval

Signature  **Date 01/03/2022**

Appendix 1: Annex 13 labelling requirements for CTIMPs

1	Name, address and telephone number of Sponsor or investigator (the main contact for information on the product, clinical trial and emergency unblinding).
2	Pharmaceutical dosage form, route of administration, quantity of dosage units (and name / identifier and strength / potency in case of open trial).
3	The batch and/or code number to identify the contents and packaging operation.
4	Trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere.
5	Trial subject identification number/treatment number and where relevant the visit number.
6	Name of investigator (if not included in 1 or 4).
7	Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject of person administering the product).
8	“For clinical trial use only” or similar wording.
9	The storage conditions.
10	The period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.
11	“Keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.