IMP Management and Accountability

SOP Reference: RGIT_SOP_026	
Version Number: 10.0	
Effective Date: 02 Aug 2024	Review by 02 Aug 2027
Author: Alina Saeed, Clinical Trial Facilitator	
Approved by: Keith Boland Senior Clinical trial Manager	Date: Keith Boland Digitally signed by Keith Boland Date: 2024.08.06 11:46:15 +01'00'

Version	Date	Reason for Change
Version 1.0	31 May 2007	Annual review
Version 2.0	20 Jun 2008	Annual review
Version 3.0	08 Feb 2010	Formation of Joint Research Office
Version 4.0	14 Jul 2011	Amendment following MHRA Inspection
Version 5.0	03 Dec 2012	Annual Review
Version 6.0	18 Feb 2015	Scheduled Review
Version 7.0	25 Oct 2017	Schedule Review Addition of: IMP transfer between sites, CI to check SmPC regularly, Contracts responsible for technical agreement, Updated: IMP Label template
Version 8.0	19 Oct 2020	Scheduled Review Templates removed and administrative changes to SOP. JRCO name change to RGIT.
Version 9.0	07 Jan 2021	Amendments due to leaving the European Union from 1st January 2021

Version 10.0	02 Aug 2024	Scheduled Review

Table of Contents

1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the management and accountability of Investigational Medicinal Products (IMPs) in clinical trials sponsored by Imperial College Academic Health Science Centre (AHSC).

2. INTRODUCTION

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 Imperial College AHSC may undertake as sponsor of a clinical trial and as such, will not be an exhaustive operating procedure on all aspects concerning IMPs in clinical trials. For example, the Imperial AHSC 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 Good Manufacturing Practice (GMP) and all checks are in place before dispatch. This documentation would normally need to be submitted for the Clinical Trial (CT) authorisation to the Regulatory body.

The trial pharmacy is responsible for granting light' approval before releasing the IMP for dispensing to the trial.

Pharmacy 'green light' can only be issued once all regulatory; MHRA in the UK; relevant ethics committee and local trusts approvals are in place to allow the dispense of the study IMP.

The green light process will include review and approval of all QP and batch release documentation to ensure regulation has been followed. This will be an ongoing process for the duration of the trial and will occur for each separate batch supplied to the research site.

This SOP will not cover local pharmacy processes/procedures for dispensing of IMPs as this will be under the remit of the pharmacy department/s in each host organisation (e.g. NHS Trust) involved in the trial. As part of the NHS controls assurance arrangements in England, a set of standards have been published on Medicines Management (safe and secure handling) against which NHS bodies report.

3. RESPONSIBILITIES

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

It is the responsibility of the Head of Research Governance and Integrity Team to ensure that this SOP is updated by the review date or as necessary.

4. PROCEDURE

4.1. **Management / supply of IMP It is the CI's responsibility to ensure that the management of the IMP is to GCP and follows the requirements set out in the Medicines for Human Use (Clinical Trials) Regulations 2004. The CI may delegate this function to the suitability qualified pharmacy lead. The CI should ensure that responsibilities of the pharmacy department have been clearly defined in the study delegation log. An example delegation log can be found in Appendix 5.1.**

The Chief Investigator (CI), with instructions from the relevant pharmaceutical company and in collaboration with the pharmacy department at the host organisation, should determine acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any 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 ideally be stored in the pharmacy department, under the supervision of trained qualified pharmacists.

The CI should ensure that written procedures are provided to the local sites involved in the clinical trial includes 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 clinical trial pharmacist.

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 clinical trial pharmacist and an updated SmPC added to the TMF. Current SmPCs can be accessed at Electronic Medicines Compendium.

For unlicensed IMPs an Investigators Brochure (IB), full Investigational Medicinal Product Dossier (IMPD) or simplified IMPD, which is used as part of the RSI must be included in the TMF and provided to the clinical trial pharmacist from the manufacturer. The CI is responsible for ensuring the IB, full or simplified IMPD 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 simplified IMPD or a full IMPD is required.

It is the responsibility of the CI to ensure that current SmPC, full or simplified IMPD/IB updates are checked regularly and any significant safety/quality changes must be submitted as substantial amendment to the regulatory bodies.

The CIClinical Trial pharmacy team in conjunction with the appropriate pharmaceutical company should:

a. Ensure timely delivery of IMP(s) to the local site(s)
b. Take steps to ensure that the IMP(s) are stable over the period of use in line with the pharmaceutical company QP clearance and stability testing.

The CI should not activate a local site and supply an investigator/institution with the IMP(s) until he/she obtains all required documentation (e.g. approval/favourable opinion from Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA) and HRA, including local trust RD approvals/CCC clearance as necessary.

For a UK clinical trial involving Investigational Medicinal Products (IMPs) imported from approved countries (initially all EU and EEA countries), the sponsor must ensure that a UK Manufacturing and Import Authorisation (MIA(IMP)) holder has an assurance system in place. This system must verify that the IMPs are certified by a Qualified Person (QP) in the origin country before trial use. The QP oversees this process but does not need to recertify the IMPs. Routine verification tasks can be delegated within the MIA(IMP) quality system. The overseeing QP may be based in the UK or an approved country. For imports from non-approved countries, QP certification must be by a UK-resident QP.

From 1 January 2022, Sponsors with a UK MIA(IMP) can perform or outsource QP certification verification. (A one-year transition period starting 1 January 2021 was provided by MHRA for compliance)

IMPs arriving in Great Britain from Northern Ireland do not need additional oversight if:

- *They are QP-certified in the EU/EEA for use at Northern Ireland sites and then supplied to Great Britain.*
- *They are certified by a Northern Ireland MIA(IMP) holder.*

IMPs from non-approved third countries still require UK QP certification and importation.

4.2. Coordination with Pharmacy Department

Pharmacy staff should be involved early in the set-up of the clinical trial. Information regarding the trial should be discussed with the pharmacy department includes:

- Purpose of the trial
- 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 final IMP (or parts of IMP if final IMP is to be assembled on pharmacy premises) and any relevant handling/Control of Substances Hazardous to Health (COSHH) data
- Source of the products to be used
- Labelling- inner and outer labelling as applicable.

- Name and contact details of CI, local investigators and others involved in organising, managing or administering the trial IMP (including trials unit if applicable)
- Oversight of trial documentation retained in pharmacy

The CI in conjunction with the pharmacy department must:

a. Maintain records that document shipment, receipt, storage, safe handling, reconstitution/dispensing, patient returns, and destruction of the IMP(s) (see RGIT_SOP_005 for essential documentation)
b. Maintain a system for retrieving IMPs and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
c. Maintain a system for the handling of unused and expired IMP(s) and for the documentation of returned IMPs.
d. Maintain sufficient quantities of the unexpired and QP tested/stable IMP(s) to be used in the trials.
e. Reconfirm IMP specifications, should this become necessary, and maintain records of batch sample analyses, characteristics and storage conditions, e.g. temperature logs. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

It is recommended that a member of the pharmacy staff should have an assigned role as pharmaceutical coordinator in relation to each CTIMP. In most cases this will be a designated clinical trials pharmacist or technician.

The Pharmacy trial file will contain protocol and all IMP related documents including all subsequent amendments. Pharmacy/Pharmacies may follow their own trust SOPs of IMP management.

4.3. Coordination with contract

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. Head of research contracts should be involved early and discuss the project to initiate the set-up of the clinical trial. RGIT Clinical Trials Manager/s should also input/review the IMP technical agreement from a Sponsor's oversight perspective.

4.4. Drug Accountability

Drug accountability logs should be kept for all CTIMPs at pharmacy level. An example log can be found in appendix 6.2 and 6.3. These logs should detail at least:

- Trial Identifiers e.g. Trial Name, EudraCT number, PI Name, Institution and IMP name
- Subject 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 as long as they meet the minimum requirement mentioned above.

For Type A category Trials (potential risk associated with the IMP no higher than that of standard care) and some Type B category Trials on a case by case basis (potential risk associated with the IMP is somewhat higher that that of standard care) a risk adapted approach for the IMP management may be adopted. If a drug accountability log is not used in this context then a risk assessment detailing the justification for this should be completed in collaboration with the sponsor.

Drug destruction arrangements should be discussed with the pharmaceutical company and the pharmacy department to determine how the process will be undertaken and agreed by the sponsor. An example drug destruction form is found in Appendix 6.4.

4.5. 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 forwarded with the application for Clinical Trials Authorisation (CTA) to the MHRA. Further details on the CTA can be found in RGIT_SOP_008.

4.3.1 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, Imperial College recommends that IMPs are labelled following the guidance of Annex 13.

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 subject
iv. For Clinical Trial Use only

Trial (EudraCT number)
Investigator: Dr xxxxxx
Product name, form and strength
Directions *(as specified by the prescriber)*
Patient name and subject code Date of Supply

Name & address of hospital/primary care supplier
Keep out of reach of children
For clinical Trial use only
Any additional cautionary label *(as recommended by the BNF)*

Note that the cautionary label "Keep out the reach of children" is a legal requirement on all UK dispensed medicines. Information on this and other cautionary and advisory labels for dispensed medicines is given in Appendix 9 of the British National Formulary (BNF).

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

Pre-existing commercial labels for Investigational Medicinal Products (IMPs) within their marketing authorization may be used in clinical trials, provided they are approved by the MHRA for trial use. However, these labels must be supplemented with an overlabel or additional information as required for the clinical trial, ensuring compliance with trial-specific requirements.

4.4.2 IMP used outside its marketing authorisation or IMP with no marking 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.

Appendix 6.5 contains full details of what should be included in a label according to Annex 13.

For Clinical Trials Use Only	
Trial Name	Trial (EudraCT number)
Product name, form and strength	
Direction of use/Instruction	
Subject Name	Visit Number:
Subject Number:	Date of supply:
Code Number/Pack Number	
Batch Number:	Retest date/Expiry date:
Storage condition	
Principal Investigator_____ Site Name:_____	
Chief Investigator: Dr xxxxxx	
Sponsor: Imperial College London/ Imperial College NHS Trust RGIT London W2 1PG	Contact Number
Keep out of reach of children	

4.4.3 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 is also likely to 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.

4.4.4. IMP transfer between sites

Once an IMP has been delivered to a site it should not subsequently be transferred to another site without first being returned to the clinical trial supply company for inspection and further QP release. The packs would then be available for delivery to another site. Documentation (quantity, locations, dates, method of transfer) on the IMP transferred should be maintained. However, in very exceptional cases (for e.g. where the safety of the subject is jeopardised if supplies are not provided from another site) IMP can be transfer between sites with a valid documentation.

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

Responsible parties for transfer of IMP between sites should be noted on the IMP technical agreement or equivalent.

4.6. Trial specific IMP SOPs

The CI, in conjunction with the pharmaceutical company and the pharmacy department at the host organisation should ensure that the following trial specific SOPs are in place before starting the trial:

- Receipt and recording of safe delivery of IMPs
- Safe handling and storage of IMPs
- Code breaking of blinded IMPs
- Preparation and dispensing of IMPs
- Return and disposal of unused and expired IMPs
- Maintaining a pharmacy study file
- Relabelling of IMPs
- Temperature monitoring

5. REFERENCES

Annex 13, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, July 2010

RGIT_SOP_005 - Essential Documentation and the Creation and Maintenance of Trial Master Files

RGIT_SOP_008 - Submitting a CTA Application to the MHRA

Regulation 37 of SI 2004/1031

ICH GCP (1996), Sections 5.12, 5.13, 5.14

Medicines for Human Use (Clinical Trials) Regulations 2004, SI: 1031, Part 6

Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994, SI3144

MHRA Risk Adapted Approaches to the Management of Clinical trials of Investigational Medicinal Products:

6. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Study Delegation Log – RGIT_TEMP_037
Appendix 2: Subject Dispensing and Return Accountability Log – RGIT_TEMP_038
Appendix 3: Drug Accountability Log – RGIT_TEMP_039
Appendix 4: IMP Destruction Log – RGIT_TEMP_040
Appendix 5: Annex 13 Labelling Requirements for CTIMPS – RGIT_TEMP_051