ECTU Central Office SOP_OP_16: Management of Trial Investigational Medicinal Product (IMP) Supplies

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Document Revision History		
Version No.	Effective Date	Summary of Revisions
1.0	28 Feb 2020	Initial creation
2.0	05 Oct 2022	SOP has been transferred onto new SOP template. • This SOP has been extensively revised throughout. Additional details have been added to procedures described in this SOP and the Trial Manager role further clarified. • Caveats have been added where appropriate to reflect ongoing changes following UK departure from EU • Added section 3 detailing responsibilities of Trial Manager • Reference section updated – URLs updated and two new supporting documents added

1.0 PURPOSE

The Medicines for Human Use (Clinical Trial) Regulation defines the Investigational Medicinal Product (IMP) as a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is,for the purposes of the trial:(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization, (b) used for an indication not included in the summary of product characteristics under the authorization for that product, or (c) used to gain further information about the form of that product as authorised under the authorization.

The purpose of this SOP is to describe the IMP management activities of CTIMP studies adopted into ECTU, where responsibility for this has been delegated to ECTU.

2.0 SCOPE

This SOP should be used for all studies adopted into ECTU that require management of trial IMP supplies, where any aspect of this task has been delegated to ECTU.
Should a Sponsor have an SOP that covers this activity, this will be followed and a file note will be produced to document that the Sponsor SOP will be followed.

This SOP applies to Individuals within the ECTU trial management team who have been delegated the management of IMP tasks by the Sponsor.

3.0 RESPONSIBILITIES

- IMP management is the responsibility of the Sponsor but they may delegate some responsibilities to the ECTU Trial management team. In this SOP tasks delegated to the Trial Manager may be performed by the Trial Manager or a designee. These will be detailed in the co-sponsorship agreement

- The Trial Manager will be involved in either developing an appropriate IMP supply management system specific to the requirements of the trial or ensuring that an appropriate system is in place via a third party

- The Trial Manager will be responsible for ensuring that IMP is released to sites only once all the appropriate approvals are in place (including Sponsor Regulatory Release, site-specific Green Light checks)

- The Trial Manager will be responsible for providing documentation to participating site pharmacies for the documentation of IMP use (for example, prescriptions, accountability logs, destruction) or ensuring that site specific documents are reviewed and approved by the Sponsor prior to use

- The Trial Manager may also be responsible for co-ordinating and documenting IMP site-site transfers if applicable following Sponsor approval.

4.0 PROCEDURE

4.1 Early assessment of status of trial IMP supplies

4.1.1 The Trial Manager should consider the following factors as early as possible in the trial planning process.

Regulatory considerations (i.e. Investigational Medicinal Product (IMP), Non-Investigational Medicinal Product (NIMP), eligibility for reduced requirements from MRC/DH/MHRA Joint Project on risk-adapted management of clinical trials of IMPs). A decision on whether a trial involves an IMP or NIMP should be made according to the MHRA algorithm 'Is it a clinical trial of a medicinal product?' (Algorithm_Clean__1_.pdf (publishing.service.gov.uk) in conjunction with the CI and Sponsor.

- Product considerations (i.e. existing commercial product with marketing authorisation in the UK or an EU state).
- Location of all involved parties (i.e. manufacturer, a third party distributor, participating sites) and potential impact on aspects such as labelling, Qualified Person (QP) release, IMP import and export duties and UK Supply Chain Oversight (SCO).
- Good Manufacturing Practice (GMP) manufacture considerations.
- Standards, specifications and manufacturing scope.
- Costings – contact procurement department if appropriate to determine potential suppliers and costs.

4.1.2 The Trial Supplies Checklist on Trial Supplies contained within the Clinical Trials Toolkit represents a detailed list that can be used for guidance but Trial Managers should be aware of significant changes to the legislative framework post-Brexit which this Checklist does not reflect (http://www.ct-toolkit.ac.uk/routemap/trial-supplies/downloads/Trial-Supplies-Guide.pdf).

4.2 Identification of manufacturers of trial IMP supplies

4.2.1 Trial Managers must ensure that all sites manufacturing an IMP into its final dosage form as well as any packaging, labelling and assembly for clinical trial use hold Manufacturers Authorisation for Investigational Medicinal Products (MIA (IMP)).

4.2.2 IMP must be Qualified Person (QP) released for clinical trial use on behalf of the Sponsor. The QP certifies that the IMP has been manufactured to Good Manufacturing Practice (GMP) standards or at least equivalent and in accordance with the Clinical Trials Authorisation (CTA) and Product Specification File. The Trial Manager must ensure that this is in place prior to its transfer to participating sites.

4.2.3 To have a technical agreement in place is the minimum requirement for ensuring compliance regarding Manufacturing Authorisation, Marketing Authorisation and the responsibilities of the Sponsor and the manufacturer of the IMP. The Trial Manager should work closely with the Sponsor contracts team to ensure that any technical agreement clearly documents product sourcing, QP responsibilities, labelling, recall procedures, approval and supply of documentation, testing and retention schedules and temperature monitoring.

4.3 Development of trial IMP supply management systems

An appropriate IMP supply management system should be in place.

The Trial Manager will be involved in either developing an appropriate IMP supply management system specific to the requirements of the trial or ensuring that an appropriate system is in place via a third party.

- If the IMP supply management system is incorporated into the electronic data collection system then the system should be robust and fully auditable with a full audit trail.
- If the IMP supply management system is provided by an external 3rd party contractor then the Trial Manager should ensure that this is fully covered by a technical agreement and that the Sponsor are notified in case a supplier audit or inspection is required
- Factors to consider when developing an IMP Supply Management System are detailed in the IMP Management Process Plan

4.3.1 Accountability of trial IMP supplies

4.3.1.1 A system to track accountability may be incorporated in the database or alternatively accountability may be recorded on paper logs at site. The level of accountability will be determined by the level of risk, as assessed by the sponsor, and will vary for each trial. Accountability logs may record the following: Subject ID; IMP bottle number; Date dispensed; Dose; Quantity dispensed; Batch number; Date returned; Quantity returned; Destruction date; Recorders initials.

4.3.1.2 The Trial Manager should ensure that participating sites are supplied with accountability documentation or, if sites wish to use their own, that these have been reviewed and approved by the Sponsor.

4.3.1.3 The Trial Manager may also be responsible, according to the terms set out in technical agreements, for providing a master reconciliation of IMP at the end of the trial, setting out details of all IMP transfers, use and destruction across all participating sites and distributors.

4.3.1.4 If there is no system to track IMP management embedded within the trial database (i.e. REDCAP) then an IMP Management Process Plan should be produced and provided to the Sponsor for approval.

4.3.2 Labelling of trial IMP supplies

4.3.2.1 For IMPs used outwith the terms of their MIA the product should continue to be labelled in compliance with the requirements provided in Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices (unless approval for reduced labelling is in place) until advised differently by the MHRA and the UK Government.

4.3.2.2 Documentation of the labelling requirements will be detailed in the technical agreement. Depending on the trial, the label template may be provided by the

manufacturer or generated by the Trial Manager and/or the Sponsor. The IMP label must be approved by the MHRA before use: http://www.ct-toolkit.ac.uk/routemap/trial-supplies/downloads/Trial-Supplies-Guide.pdf should be consulted for more guidance.

4.4 Shipment of trial IMP supplies

4.4.1 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 site on behalf the Sponsor. Contracts for IMP delivery are usually between the manufacturer and the distribution company or the Sponsor and the distribution company and will be detailed in the technical agreement.

4.4.2 Organising shipments may be delegated to the Trial Manager, the delegation of responsibilities table in the sponsorship agreement and any additional technical agreements or contracts should detail who is responsible for the various aspects of IMP management. The task of documenting shipments and ensuring that delivery receipts and, as appropriate, evidence of temperature control during transit may be delegated to the Trial Manager (further detailed in 4.4.6).

4.4.3 Shipping of trial IMP supplies to sites will be conducted by the drug manufacturer or by a distribution company on receipt of an IMP supplies order form once all relevant regulatory approvals are in place. These include Research Ethics Committee (REC) favourable opinion and a Clinical Trials Authorisation (CTA) has been granted in the applicable territory(ies), as well as NHS R&D/C&C Management approval being in place as applicable.

4.4.4 IMPs should remain under the control of the manufacturer and/or distributor until completion of a two-step release procedure:

- certification by the QP (technical release) and
- authorisation to the CI ('Regulatory Checks Complete').

Both releases should be documented and the paperwork retained in the Trial Master File.

4.4.5 Unblinding arrangements will be detailed in the protocol. These should be made available to the appropriate responsible personnel before IMPs are shipped to sites, typically by the drug manufacturer or distribution company.

4.4.6. Shipments to sites can commence only after Regulatory Green Light is granted by the Clinical Trial Monitor.

4.4.7 A detailed record of shipments made by the manufacturer or importer should be maintained by the Trial Manager as part of the Trial Master File. Details in relation to whom the shipment is addressed and delivered to, records of receipt and evidence of temperature monitoring, should be filed as appropriate. Evidence of temperature monitoring (where relevant), should if possible, be a print-out/download of a log from a temperature monitor. Responsibility for receipting and checking that IMP is within the correct temperature range lies with the site pharmacy.

4.4.8 The Trial Manager may be responsible for review of stock levels and reordering of IMP for sites in conjunction with site pharmacies and distribution companies. OP-T02 IMP Management Plan and OP-T03 Stock Review Log should be used unless already covered by processes or documentation provided by Sponsor, manufacturer or distributor.

4.5 Receipt of trial supplies

4.5.1 Where the drug manufacturer contracts a distribution company to ship IMP to sites, a drug supply agreement will detail the checks to be carried out on receipt of the IMP. The shipment form is then sent to the distribution company.

4.5.2 The Trial Manager is responsible for ensuring that there is evidence of the order and receipt of IMP supplies to participating sites.

4.6 Storage of trial supplies

4.6.1 The Trial Manager must ensure as part of the site feasibility and set-up process that supplies can be stored at sites under appropriate conditions as specified by the study SPC and/or IB.

4.6.2 Pharmacies must have facilities that allow for trial supplies to be stored separately from normal pharmacy stock in areas with restricted access. If IMP is stored outwith a pharmacy then the PI must ensure that a local risk assessment is available for review by the Clinical Trials Monitor as part of the SATO

4.6.3 Storage instructions should be provided to each site by the TM either in the pharmacy file (if applicable) or in the SPC booklet or simplified IB. These should include information about the temperature range or light conditions. It is the responsibility of the PI to ensure that the supplies are managed and used correctly at their site. Any pharmacy manual/IMP handling instruction should be reviewed prior to use by the Clinical Trial Monitor.

4.6.4 If there is requirement to monitor the storage temperature, the TM is responsible for informing the PI, of their responsibility to ensure that a temperature log is maintained with temperatures recorded by a calibrated temperature recording device. Where possible, this device should be linked to an alarm system which alerts the user when the temperatures fall out of range. The TM should inform site teams that evidence of regular maintenance and recalibration of temperature monitoring equipment should be available on request for monitoring.

4.6.5 Where a temperature deviation is recorded, this should be reported to and recorded by the Trial Manager and the site instructed to quarantine the affected IMP under the appropriate storage conditions. The Trial Manager should inform the Clinical Trials Monitor as well as the manufacturer or distributor as per the technical agreements in place.

4.6.6 Temperature deviations will be recorded as a deviation/violation as appropriate.

4.7 Participant use of trial supplies

4.7.1 In trials where the drug is supplied directly to participants the Principal Investigator should explain the correct use and storage of the trial supplies to each participant at the start of the trial and should check, at intervals appropriate to the trial, that each participant is following the instructions properly. The TM may be responsible for supplying instructions to sites and ensuring training is available if applicable.

4.7.2 The participants should be instructed to return all unused supplies including empty containers at each visit (or as detailed within the current trial protocol). The supplies returned from each participant should be reconciled against the dispensed supplies as appropriate allowing the supplies used by each participant to be calculated. Copies of the reconciliation paperwork should be sent to the Trial Manager and filed in the TMF.

4.8 Return or destruction of trial supplies

At the end of the trial overall reconciliation of trial IMP supply documentation must be carried out and this may be delegated to the Trial Manager.

- Any discrepancies should be reported to the Sponsor.
- If supplies are to be destroyed then a record of the date of destruction and the personnel responsible will be kept.
- A copy of the destruction records should be sent to ECTU and filed in the TMF.

4.9 Recalls

Procedures for retrieving trial supplies and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. These procedures will be detailed in the drug supply agreement or manufacturer's agreement.

4.10 Re-allocation of trial supplies

4.10.1 Trial supplies must not be re-allocated or transferred to another site unless in exceptional circumstances.

4.10.2 If reallocation between sites is required the Trial Manager should discuss and gain agreement from the Sponsor and drug manufacturer before transferring trial supplies following the process detailed in the sponsor SOP.

4.10.3 All documentation concerning re-allocation of supplies must be retained in the site file and TMF, including evidence of any shipment receipts and temperature monitoring, as appropriate.

4.11 Randomisation procedures and unblinding

4.11.1 The Trial Manager should ensure that the process of generation, security, distribution, handling and retention of any randomisation or identification code used for packaging trial supplies and code-break mechanisms is documented and filed in the TMF. They should also ensure that there is a clear record of all unblinding requests maintained in the Trial Master File and evidence of compliance with the unblinding procedure.

4.11.2 Unblinding procedures will vary across trials but should be detailed in the protocol.

4.11.3 The participant's welfare must always take priority over any other consideration in determining when a code break should be revealed. Except in the case of an emergency, the code-break should only be revealed with the agreement of the Sponsor.

4.12 Incident reporting

Incidents that occur as part of the trial and affecting IMP supplies should be documented as protocol deviations and/or protocol violations and submitted to the sponsor by the site. The site will be advised to inform the Trial Manager of any deviations/violations related to IMP supplies that are reported. All temperature excursions must be reported to the Sponsor monitoring team and a log maintained by the TM within the TMF.

5.0 RELEVANT DOCUMENTS AND REFERENCES

MHRA algorithm 'Is it a clinical trial of a medicinal product?'
Algorithm_Clean__1_.pdf (publishing.service.gov.uk)

Clinical Trials Toolkit on Trial Supplies (http://www.ct-toolkit.ac.uk/routemap/trial-supplies/downloads/Trial-Supplies-Guide.pdf)

The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices (Volume 4): Annex 13
http://www.it-asso.com/gxp/eudralex_v27/contents/vol-4/2009_06_annex13.pdf

OP-T02 IMP Management Plan (on shared drive)

OP-T03 Stock Review Log (on shared drive)

GS010 ACCORD Sponsor IMP/Intervention Management