Royal Papworth Hospital
NHS Foundation Trust

Document Title: Sourcing of Investigational Medicinal Products for Royal Papworth Sponsored Studies: Considerations for Manufacturing, Procurement, Assembly and Labelling

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Summary of Amendments

Version:	Modification:
3.0	Title of SOP changed. Amendments made with regard to Brexit
4.0	Amendments throughout

Key Points of this Document

- This document sets out the procedures to be followed for the manufacture, assembly, packaging and labelling of an Investigational Medicinal Product (IMP).
    - Manufacture: Describes any process involved in the production of the final formulated medicinal product including the final packaging and labelling. The whole process must be completed according to Good Manufacturing Practice. Any party undertaking manufacture of an IMP must have the appropriate licence (MIA(IMP)).
- Manufacture does not include the process of dispersing, mixing, diluting or mixing the IMP in a vehicle for the purpose of administration.
    - Assembly: Refers to aspects of the manufacturing process that include packing the product down from bulk stock and labelling it for supply within a clinical trial or over labelling a product already in its final container for a clinical trial. These aspects can be conducted without a MIA (IMP) under the Regulation 37 exemption.
- This applies to all IMPs where Royal Papworth Hospital NHS Foundation Trust is to act as the sponsor or co-sponsor for trials involving an IMP.
- This SOP complies with the principles of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) annex 13, and complies with the UK Medicines for Human Use (Clinical Trial) Regulations.

1 Purpose and contents of this document

a. To provide an outline of the processes required prior to the Clinical Trial Authorisation (CTA) approval regarding IMP sourcing, manufacture, assembly, packaging, and labelling.

b. To establish the roles and responsibilities of members of the research team and which roles can be delegated with regard to IMPs.

c. To provide guidance on how IMPs should be supplied for use within NHS research facilities in accordance with current regulations.

d. To provide guidance on the contracts required when sub-contracting IMP manufacturing or assembly activities outside of Royal Papworth NHS Trust.

2 Roles and responsibilities

a. This SOP should be consulted by the research team in conjunction with the pharmacy clinical trials team at the planning stage of the research (prior to CTA submission and protocol development).

b. It is the investigators and sponsors responsibility to ensure the IMP (including active comparators and placebos) is manufactured in accordance with any applicable GMP and has appropriate labelling that does not reveal blinding where applicable. Trial specific labelling should comply with regulatory requirements (GMP Annex 13).

c. The investigator and sponsor are also responsible for ensuring that IMP is sourced from appropriate manufacturers with adequate licenses for the manufacture of IMP i.e. a MIA(IMP) and that it is packaged appropriately to prevent contamination and deterioration during transport and storage.

d. Whilst it will remain the investigators responsibility for the above tasks they may be delegated to the clinical trials pharmacy team who must be involved at the earliest stage possible.

e. The pharmacy clinical trials team are responsible for ensuring that the investigator is advised appropriately in the matters relating to the sourcing, manufacture, assembly and labelling of clinical trial investigational material.

f. The pharmacy clinical trials team will keep the research team updated with regard to expected timeframes and costs, however the use of external suppliers and contractors may result in extended timeframes and increased costs from initial projection.

g. The Pharmacy department at Royal Papworth does not hold any licenses for IMP manufacture or importation (of any drug) and therefore the use of a third party subcontractor will be required for any IMP sourced directly for clinical trial use by the Trust (unless the IMP already has a MA in the UK).

3 Policy

a. All staff involved in active research should be aware of this SOP at the outset of the research project. R&D Staff and all pharmacy staff should be aware of this SOP. Failure to follow this SOP may result in disciplinary procedures.

4 Procedure

4.1 General points to consider with IMP supply:

a. At the initial meeting with the investigator (or delegate) and the pharmacy clinical trials team, the supply of IMP should be discussed along with the ordering and purchasing arrangements.

4.2 Supplies may be sourced through a number of routes:

a. Commercial supply – for licensed products that do not require repackaging general pharmacy stock may be suitable. NB if the product is supplied as generic stock (where the manufacturer may vary) the sponsor should consider whether or not it is suitable for use in the trial or if a single supplier/brand should be identified.

b. Commercial supply - where a manufacturer has agreed to supply stock free of charge for trial purposes but where the manufacturer is not the sponsor. In this scenario the Sponsor must verify that the trial has the appropriate authorisations and that the products have been manufactured in accordance with GMP. An agreement should be set up defining the division of responsibilities prior to supplies being made.

c. Non-commercial supply – for products without a manufacturing authorisation which need to be released by a Qualified Person (QP) for trial specific use. A third party subcontractor will be required if any manufacturing activity is required before the IMP can be used for trial purposes. See SOP066; Subcontracting of Research Activities. A technical agreement should be in place before any supplies are obtained.

d. All IMPs should be supplied to the pharmacy clinical trials department. When IMP is available for use it should not be released by the pharmacy until all required regulatory approvals have been obtained.

4.3 Planning Stage

The chief investigator or delegate should have a discussion with the pharmacy clinical trials team prior to the CTA submission as these discussions will have a bearing on total trial costs. The following information should be established:

a. Names of all IMPs, comparator products and placebos

b. Nature of IMPs – licensed, unlicensed, off-label, non-medicinal. An initial assessment of the material should be undertaken to identify any concerns with the product. The assessment

should cover sourcing, manufacture, storage, handling, dosing and product availability. It is not a clinical risk assessment. See FRM077.

c. Proposed treatment schedule, dispensing visits, visit windows, estimated patient numbers etc as this will affect required quantity, pack sizes and labelling.

d. In the case of blinded studies:

   1. Whether a matched placebo is required and how will this be achieved.

   2. How the trial will be unblinded – are randomisation unblinding envelopes required from the manufacturer.

e. The manufacturers/suppliers should be identified.

f. Consideration as to additional facilities and staffing required for drug storage, preparation and administration.

g. If the study is a multicentre trial, how will IMP be delivered to the sites i.e direct from manufacturer or via RPH with the sponsor pharmacy acting as a hub.

h. If an Investigators Brochure (IB) or Summary of manufacturers Product Characteristics (SmPC) is available.

i. If an Investigational Material Product Dossier is available (IMPD) or if an abbreviated IMPD can be used. See the MHRA website for further guidance on IMPDs.

j. Location for IMP storage – if pharmacy is not a suitable location then a suitable storage location should be identified and approved by pharmacy prior to commencement of the study.

k. If any re-labelling, re-packaging or assembly is required whether or not it is possible to be carried out under exemption 37 (see Appendix 1).

l. If trial-specific Certification by the Qualified Person (QP) is required: this will depend on the licence status of the IMP, where it is made and what agreements are in place with the manufacturer i.e whether the manufacturer will provide Certification by the QP of the product for the study. Note that Certification by the QP (technical release) is required:

   1. on all products specifically manufactured for use in the trial including placebo.

   2. on products that require a change from authorised product presentation i.e. over encapsulation.

3. on all products that have been packaged and/or labelled according to a randomisation list.

4. For products that are imported from the EU or EEA a licensed importer is required, the importer will need to provide assurance that the product has been certified by a Qualified Person (QP) in a listed country, before release to trial sites. The list of approved countries will initially include all EU and EEA countries.

5. On any product imported from outside the EU Certification by the QP of the product must be conducted by a UK registered qualified person (QP declaration of equivalence to EU GMP required in addition to QP certification)

m. QP release is not required:

1. for commercially available products that are used within their original packaging.

2. For products that undergo assembly (i.e. change to packaging or labelling), as long as these are changes authorised under the Regulation 37 exemption. (NB labelling according to a randomisation list is considered to be manufacturing).

See Appendix 1 for what constitutes manufacturing and what constitutes assembly.

4.4 Researchers looking to use products for studies that do not require MHRA approval for clinical trial research e.g physiological studies

a. The pharmacy department should be involved to the same degree when sourcing materials for human administration at Royal Papworth and local policies and procedures should be applied when procuring such items for the first time. Unlicensed products should be reviewed and risk assessed by a pharmacist before a shipment is requested and pharmacy should retain the role of receiving (always) and storing (where this is feasible) shipments of products.

5 Labelling/re-labelling of IMP's

a. All trial specific labelling activities for IMP's must be compliant with GMP Annex 13

b. All IMP's should be labelled to allow for the proper use and identification of the product. (see below for the minimum labelling requirements)

1. Minimum labelling requirements for IMP's to be included on the label (See MHRA guidance: Labelling of Investigational Medicinal Products)

a. name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency un-blinding);

b. pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

c. the batch and/or code number to identify the contents and packaging operation;

d. a EudraCT trial reference code;

e. the trial subject identification number/treatment number and where relevant, the visit number;

f. directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);

- "For clinical trial use only" or similar wording;
- the storage conditions;
- 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.
- "Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

c. Labels should be designed and included in the Clinical Trials Application (CTA). If trial specific labelling is not to be used adequate reasoning should be supplied in the CTA.

d. Pharmacy may be delegated the task of label design by the investigator.

e. The Medicines for Human Use (Clinical Trials) regulation 46 (2) allows for a situation where trial specific labelling is not required; this applies if the IMP is

1. used within the terms of its licence as part of an open label trial,

2. dispensed to a subject in accordance with a prescription written by an authorised health care professional and

3. labelled in accordance with UK regulations for dispensed medicinal products (Medicines for Human Use Schedule 5 (SI 1994/3/94))

f. Labelling is usually performed at the manufacturing stage and included in the Certification by QP . In some instances, it is necessary for some labelling to be carried out post Certification by QP, commonly when the labelled product is reconstituted into a syringe or infusion bag for administration, in this case a label should be applied that is compliant with local hospital procedures to ensure the safe identification of the patient and the product.

g. Post Certification by QP, labelling may also be undertaken by pharmacy or under the supervision of a pharmacist in the following circumstances:

1. Application of expiry date labelling (or revised expiry date labelling)

2. Application of an investigator name

3. Application of a protocol number

h. It is expected that the level of assurance of the quality of the final product should not be less than if this labelling were performed prior to Certification by QP. Pharmacy must have appropriate procedures in place to cover labelling of IMP.

5.1 Blinding of IMP

a. For trials sponsored by Royal Papworth, where a double blinded protocol is to be followed, the IMP will require labelling, randomising and re-packaging. This service must be contracted out as this is classed as manufacture rather than assembly. A Technical agreement should be set up with the Sponsor and the vendor/contractor in conjunction with Pharmacy Clinical Trials who will facilitate the process.

6 Choosing a Sub-contractor

a. SOP066 Subcontracting of Research Activities should be followed when looking to sub-contract IMP related work outside of Royal Papworth NHS Trust.

b. It is good practice to obtain quotes for work to be undertaken from a number of suitable contractors. The final decision to use a specific contractor should be based upon some or all of the following criteria:

1. Appropriate licenses and qualified personnel in place
2. The contractor shows a full understanding of the services required
3. Royal Papworth has experience of working with the contractor previously or the contractor demonstrates experience of working on similar trials
4. Visits made to the premises of the potential contractors and outcomes (if necessary)
5. The estimated quote
6. Recommendation by another Trust/clinical trials unit working on similar trials

c. Once a contractor has been chosen and the trial has regulatory approval the necessary contracts will need to be formalised.

d. A Technical Agreement (TA) should exist between the sponsor and the contractor designating all the arrangements made for the manufacturing/assembly process and responsibilities undertaken by the contractor and those retained by the Sponsor.

e. Where medication is provided free of charge by a manufacturer who is not acting as the sponsor, an agreement between the manufacturer and the sponsor will be required. If subsequent manufacturing/assembly work is required a second contract should exist between the sponsor and the contractor.

7 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Sponsor and Site Files.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: (this version)	Current approved version date
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2018)
Key related documents:	Trust Research Policy Pharmacy Internal Procedure for the Dispensing of Medicines. SOP022 Clinical Trials Supply management SOP030 Roles and Responsibilities/Delegation Log SOP069 Emergency Unblinding & Codebreaking of Clinical Trials SOP018 Randomisation of Papworth Sponsored Clinical Trials, CT015 Authorisation of IMP(Investigational Medicinal Product) storage areas outside of the Pharmacy Clinical Trials Department, SOP066 Subcontracting of Research Activities, GCP, GMP & Uk Medicines for Human Use (Clinical Trial) Regulations MHRA website, Pharmacy Clinical Trial Activities 2009 UK Clinical Trial Regulation, Appendix 1, Appendix 2 UK Policy Framework for Health and Social Care Research (2018)

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	No	No	No	No	No	No	No
Positive/Negative	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Review date:			September 2025				

I certify the contents of this SOP has been reviewed and ratified

DocuSigned by:
Dr Patrick Calvert
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Signed by Dr Patrick Calvert, Clinical Director of R&D

12-Sep-2022

Date

Appendix 1

Brief advice on Certification by QP requirements and working under exemption 37: See the MHRA Good Clinical Practice Guide for detailed information on the trial specific release process.

UK and EU licensed drugs used within the terms of their license do not need trial specific QP release as this is provided by the Marketing Authorisation (MA) and the accompanying Product License (PL) when the drug is used with its approved packaging and labelling. The MA can be UK or EU specific.

If a product has a UK or EU license but is not to be used within the terms of its license or its original presentation or packaging, then depending on the activity to be undertaken (manufacture or assembly) it may or may not need a trial specific QP release. Manufacturing activities will require a QP release by an MIA(IMP) license holder. Assembly activities can be undertaken under the UK Clinical Trial Regulation (section 37 exemption) and an MIA(IMP) is not required as long as the assembled product is used exclusively within the hospital or trial sites for which the trial has been approved.

If a product does not have a UK or EU license then it will require trial specific QP release, furthermore if the product is manufactured outside of the EU, a QP must make an additional declaration that the product has been manufactured to EU GMP equivalent standards.

Manufacturing activities include:

- Importation from outside of the EU
- Filling of capsule or over encapsulation of tablets or capsules
- Weighing of IMP, addition of water and pH stabilisation
- Mixing of IMP with other agents and formulating into unit doses
    - Preparing liquids for oral or external use. Manufacture does not include the process of dispersing, mixing, diluting or mixing the IMP in a vehicle for the purpose of administration.
- Filling of ampoules, vials, eye drop bottles or infusion bags (not diluting)
- Mixing of creams or ointments
- Solid dose production i.e. tablets, suppositories etc
- Filling of aerosols
- Medical gasses

Assembly activities include:

- Dispensing from bulk containers into individual subject packs or batches for specific subject use.
- Dispensing from bulk containers into non-subject specific batches for bulk storage where subject specific details are added at the time of dispensing.
- Reconstitution of IMP and transfer to syringe/bag, labelling with subject number against a prescription.
- Labelling any of the above with approved Annex 13 compliant labels.

NB: where a product is simply dispensed to an individual subject pack or reconstituted and administered immediately on the ward, this is dispensing or reconstitution only and not assembly.

Under the exemption, pharmacy are able to re-package, re-label or dispense non-patient specific batches from bulk IMP for UK and EU authorised products and products that have had trial specific QP release. Assembly of IMP may also be carried out by a doctor or person acting under the supervision of a pharmacist. All personnel should be named on the delegation log for such activities. All details of assembly activities should be established as soon as possible and included on the CTA.

Where trial material may need to be accessed immediately or out of hours and stock is held outside of the pharmacy, delegated staff may issue pre-packaged, pre-labelled IMP to which the patients name and subject number is added.

Once the above information has been established, the information will be retained in the Pharmacy File and the Sponsor and/or Site File. The information should also be added into the trial protocol and used to complete the CTA application.

Appendix 2:

Brief advice on nIMPs:

Non-Investigational Medicinal Products (nIMPs) are products sourced for research purposes that fall outside of clinical trial requirements

A nIMP can include medication used within a trial that is administered as a rescue agent, a challenge agent, background treatment or a diagnostic agent (as long as it is not the agent being assessed)

The sourcing, manufacture and assembly of non-investigational medicinal products should be carried out with a similar level of diligence as IMPs, to ensure that all trial material is of a suitable quality and that the safety of the subjects is ensured.

> When NIMPs do not have a marketing authorization in the EU, appropriate GMP requirements foreseen for the safety of the patients should still be applied and the sponsor should ensure that NIMPs are of appropriate quality for the purposes of the trial, taking into account, among other things, the source of the raw materials and any repackaging. To meet the requirements of Articles 3(2) and as referred to in Article 6(3) of Directive 2001/20/EC relating to protection of the trial subject, the same level of quality and safety should be ensured for the NIMPs as for the IMPS used in the trials.
>
> Clinical trials, Directive 2001/20/EC, Rev 1 March 2011 NIMPs