STANDARD OPERATING PROCEDURE FOR MANUFACTURE, ASSEMBLY, PACKAGING AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

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1. PURPOSE

This document describes the definitions and procedures for the manufacture, assembly, packaging, and labelling of Investigational Medicinal Products (IMP). This Standard Operating Procedure (SOP) complies with the principles of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) (Annexe 13) and complies with the UK Medicines for Human Use (Clinical Trials) Regulations.

2. SCOPE

This SOP will apply to all University of Dundee or NHS Tayside personnel (including clinical trial pharmacy staff and research personnel) who are involved in the processes of assembly, packaging, and labelling of IMPs.

3. RESPONSIBILITIES

It is the responsibility of the Sponsor to ensure that the IMP, including any active comparator and placebo, is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling must comply with applicable regulatory requirements and the IMP must be packaged to prevent contamination and unacceptable deterioration during transport and storage.

4. PROCEDURE

4.1 Introduction

This SOP should be consulted by Clinical Trial Pharmacy Staff and trial personnel at the Clinical Trial of Investigational Medicinal Product (CTIMP) planning stage (preferably before submission of a grant) to ensure early consideration of all issues pertaining to the manufacture, assembly, packaging and labelling of the IMPs and that the appropriate actions are taken.

4.2 Early-stage planning

The Chief Investigator (CI) or delegate should consider (preferably before submission of the grant) issues relating to IMP management. The following information should be ascertained:

- Names of IMPs to be used in CTIMP.
- Is the CTIMP blinded? Establish how 24-hour emergency unblinding cover will be provided.
- Manufacturer/Supplier of both active drug and any placebo.
- Storage conditions/stability issues/special handling restrictions. See TASC SOP39.
- Will the IMP be required at multiple sites? See TASC SOP39.
- An Investigator Brochure (IB) or Summary of Medicinal Product Characteristics (SmPC) should be obtained.
- Who will place the order for the IMP, what quantity will be required and who is funding this? See TASC SOP39.
- Will IMP be stored, supplied and/or dispensed from pharmacy or will this be managed, in a local IMP Storage and Supply Site by the investigator? See TASC SOP39. ***Note: IMP Storage and Supply Sites are subject to annual audit by the Clinical Trial Section of Ninewells Hospital Pharmacy.***
- Will any re-labelling, re-packaging or re-assembly be required at site?
- Will a trial-specific Qualified Person (QP) release be provided by the manufacturer?

For licensed drugs, quality assurance is provided by the Marketing Authorisation (MA) and the accompanying Product License (PL) but only if the IMP is used in the original packaged or presented form.

If licensed drug is re-packaged or presented differently for use in a CTIMP, or un-licensed drug is being used, then trial specific QP release must be provided by the manufacturer. The QP is the Quality Control expert at the manufacturing company, who confirms the quality of the IMP for use in the CTIMP.

Suppliers of IMPs must have a specific 'Manufacturing Authorisation' (MA) issued by the licensing authority before they can manufacture, assemble, or import an IMP for use in a clinical trial. However, an exemption exists in the UK Clinical Trials Regulations (section 37), which permits the assembly of an IMP in the pharmacy or locally within the trial site, by a doctor or pharmacist or person acting under the supervision of a pharmacist. The term assembly includes the reconstitution of a product or the re-packaging and/or re-labelling of a product into its final form – this exemption only applies when the IMP is assembled exclusively for use in that hospital or health centre trial site or any other hospital or health centre which is a trial site for the clinical trial in which the IMP is to be used.

This exemption means that Pharmacy can re-package, re-label or dispense batches of IMPs after they have been sourced and obtained for use in a CTIMP.

However, there is no objection to members of the study team, who have been

delegated to do so identifying and issuing a pre-packaged, pre-labelled IMP to which they have attached the participant's name and date of supply.

The Clinical Trials Pharmacy Staff may assist the CI in answering the above questions. The information should be documented and filed in Pharmacy Site File (PSF) and the Trial Master File (TMF) and/or Investigator Site File (ISF), as appropriate. The information should also be added to the IMP handling guidelines or the IMP section of the protocol.

4.3. Assembly, packaging, and labelling issues identified

If it is apparent that the IMP for a clinical trial will require some form of assembly at site (this includes the re-constitution of a product), re-packaging, or re-labelling (other than solely the application of a label containing patient's name and date of supply) then the trials pharmacist must be contacted, and the following procedures implemented:

4.3.1. Procedures for assembly, packaging, and labelling at site

Exemption 37

Ensure that any activities lie within exemption 37 of the UK Clinical Trial Statutory Instrument (SI) before commencing. If the activities lie out with the exemption, they will be classed as manufacturing and the trial team must employ an organisation with a manufacturing license to conduct the activities.

Documentation required

Ensure that the manufacturer, supplier or manufacturing organisation provides the required documentation (IB or SmPC, batch analysis certificates and QP release/shipping documentation).

Document names and signatures of personnel who will perform the assembly activities, on the Delegation log.

Document details of the IMP assembled i.e., name of IMP, quantities assembled, details of re-labelling and/or re-packaging and other pertinent details. This information should be filed in the PSF, TMF and/or ISF, as appropriate.

Assembly will take place in pharmacy.

Labelling/re-labelling

Clinical trials pharmacist will ensure that the labelling/re-labelling complies with GMP Annexe 13 revision.

For a detailed account of the labelling requirements for IMPs see the ct-toolkit website.

The law requires that clinical trial drugs be labelled in a way that allows for their proper use and identification of the product, the trial and the trial participant. It must be possible to identify and trace any IMP supplied to a trial participant for which purpose it is necessary to maintain a record of the manufacturer/supplier and batch number. This is an important safety issue in the event of an unblinding or a drug recall that may be issued at any stage during the course of the trial.

For trials in which the IMP is supplied by an outside agency (pharmaceutical company or other licensed manufacturer), the IMP should be provided with the necessary labelling in place.
In an open-label study, the manufacturer's original label might suffice if an additional label is affixed that includes the following:

- The words 'For Clinical Trials Use Only'.
- Trial participant name/initials/trial number.
- Trial reference code (e.g. EudraCT No/NHS R&D No.) to allow identification of the trial site, the CI/Principal Investigator (PI) and Sponsor.
- Directions for use or, if lengthy or variable, these may be written on an accompanying leaflet with the words 'As directed, see accompanying leaflet' added to the label.
- Specific storage information and any relevant expiry date.
- Date of issue.
- Name/address of hospital/primary care supplier.
- The words 'Keep out of the reach and sight of children'.
- Any additional cautionary label recommended by the British National Formulary (BNF).

The above also applies in a blinded trial, irrespective of whether the IMP is the test drug, comparator or placebo.

It DOES NOT apply to IMPs prescribed in accordance with their MA in an open label trial or an observational study where this is effectively carried out as part of usual care.

5. ABBREVIATIONS & DEFINITIONS

BNF	British National Formulary
CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MA	Manufacturing Authorisation
PI	Principal Investigator
PL	Product Licence
PSF	Pharmacy Site File
QP	Qualified Person

SI	Statutory Instrument
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
TMF	Trial Master File

6. ASSOCIATED DOCUMENTS & REFERENCES

TASC SOP39: IMP transport and storage

7. DOCUMENT HISTORY

History prior to 2021 is in the archived SOPs available from TASC Quality Assurance Dept.

Version Number:	Reviewed By (Job Title):	Effective Date:	Details of editions made:
7	Tracy Petrie (Quality Assurance Support Officer)	01/02/2021	Uploaded to new TASC SOP template which shows the new TASC website in the footer. Physical scan converted to electronic pdf as a requirement for upload to new TASC website
8	Shona Carson (Clinical Trials Pharmacist)	08/04/2021	Scheduled review, no changes to procedure required.
9	Shona Carson (Clinical Trials Pharmacist)	08/04/2023	Scheduled review, no changes to procedure required.

8. APPROVALS

Approved by:	Date:
Dr Valerie Godfrey, TASC Quality Assurance Manager, on behalf of TASC Clinical Research Guidelines Committee	04 Apr 2023