1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for managing investigational medicinal product (IMP) and auxiliary medicinal product (AxMP) during clinical trials.

This SOP ensures compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations, specified in the SOP Legislation and guidelines.

2 SCOPE

This SOP is valid for all clinical drug trials sponsored by hospitals that have implemented the NorCRIN SOPs.

3 RESPONSIBILITIES

The sponsor has overall responsibility for ensuring that this SOP is followed.

The sponsor's responsibilities shall be described in the quality system of the sponsor institution. Tasks are delegated according to SOP Roles and Responsibilities in clinical trials implemented in the institution.

The project leader has the responsibility for managing medicinal products in all participating centres.

The principal investigator is responsible for the medicinal products and the associated records at each centre.

The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a third party vendor such as a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf. Transfer of duties shall be specified in a written agreement.

4 PROCEDURES

4.1 Receipt of medication at the centre/hospital

This section does not apply when shelf products are used.

When the a delivery takes place, the site staff should ensure that all required procedures are followed.

An import lisence is required for shipment of clinical trial drugs if shipped from abroad directly. The hospital pharmacies have such licences and can be contacted for import. If import licence is held by a pharma company providing the drug, it can be shipped directly to site.

All IMPs must be checked against shipping documents upon arrival. The acknowledgement of receipt will be sent to sender as agreed. Shipping documentation will be filed in the investigator's site file (ISF).

Temperature logs and, if applicable, other storage conditions during transport should be checked. In case of a temperature deviation or other issues, the whole shipment will be quarantined while awaiting clarification as to whether or not the IMP can be used. Documentation related to quarantined products will be filed in the ISF.

For IMPs, produced or packaged specifically for the trial, documentation required by Good Manufacturing Practice (GMP) guidelines must be provided with each batch (lot).

Receipt of AxMP without market authorisation will be handled in the same way as IMPs.

4.2 Labelling of Trial Medication

Labelling of investigational medicinal product will be carried out in compliance with SOP Investigational Medicinal Product (IMP) at Trial Start.

Any re-labelling and expiry date extension of the IMP and unauthorised AxMP must be documented and carried out in accordance with current GMP regulations. This is considered to be part of manufacturing and requires the appropriate authorisation. For IMPs to be used in Noway, the Norwegian Medicines Agency (NoMA, SLV) can authorise clinical trial centres, investigators, sponsor or other company that handle drugs to relabel with expiry data extension.

4.3 Medicinal Product Records

All IMPs must be accounted for. IMP should be traceable throughout the trial, from manufacture to use and return. There is the same requirement for documentation of marketed drugs. Manufacturers, wholesalers and pharmacies should be able to provide documentation related to manufacture and storage of products before the investigational medicinal product is delivered to the investigator by the pharmacy.

All processes must be recorded using the agreed accounting forms and procedures.

The use of AxMP will only be documented in the Case Record Form (CRF) for each patient. AxMP without marketing authorisation should be accounted for in the same way as IMPs.

4.4 Investigational Medicinal Product Storage

IMP should be stored in compliance with the storage conditions specified in the Investigator's Brochure or SmPC.

Temperature logs must be kept for locations where IMP is stored, regardless of storage conditions.

Temperature must be monitored using suitable, validated temperature monitoring systems. It is recommended that the maximum and minimum temperatures are recorded each working day for all products.

For storage in refridgerators the temperature device should be read in small amounts of glycerol or water to avoide false increases by opening the refridgerator door for short periods (the temperature of the IMP does not increase equivalent too the increease in air for a few minutes)

IMP should be stored with limited access, e.g. in a locked room or locked cupboard and separate from other medicines.

If IMP for more than one trial is stored in the same area, the IMP for each trial must be kept separate and the storage area must be clearly labelled with the trial number/code.

Returned IMP should be stored securely and locked in a designated and labelled storage space, clearly separated from other IMP / other medicines and unused IMP.

Deviations from storage conditions must be documented (e.g. protocol deviation with a copy of temperature log) and the continued shelf life of the IMP must be assessed in each case. Products stored outside the required temperature range for more than a few minutes will be quarantined by placing them in a separate storage space labelled “quarantined”.

The project leader or manufacturers must be contacted to assess the impact of temperature deviations before the quarantined product is used. The quarantined product will only be returned to the location for unused product once written confirmation has been received from the manufacturer, that they are released from quarantine.

4.5 Randomisation

Randomisation and blinding of IMP will be documented and carried out in compliance with the agreed procedures for the project. See SOP Randomisation, Blinding and Unblinding.

4.6 Requisitions

The request for IMP from a pharmacy must be made by a medical doctor and this must be documented. Requests cannot be delegated to nurses or other trial staff.

Requisition of IMP from a pharmacy must be made in writing. The IMP Requisition form can be used. The requisition form will be filed. Requests can also be made electronically, for example, using CMS or Cytodose to requisition cytostatics. Procedures for electronic signatures established at the individual hospital must be followed. Requisition forms shall be dated and signed by the investigator.

4.7 Dispensing

IMP should be dispensed to trial subjects at the pharmacy or trial centre.

IMP must only be dispensed to subjects who have consented to the trial and are eligible (passed all inclusion/exclusion requirements).

Dispensing should be documented. Note that the batch number for IMP taken by each individual patients need to be documented.

Only trial staff who have been delegated the task may dispense IMP.

If the IMP is to be labelled further prior to dispensing, this should be done in accordance with written procedures.

Trial subjects shall receive sufficient information regarding the correct use and storage of the IMP during dispensing and should be documented in the medical records.

4.8 Shipping of trial medication

If dispensing in person is not possible, the IMP can be sent to the subject by mail or other means of transport. Mail consignments must be packed properly and sent in accordance with the regulations for handling of the drugs. Procedures for shipment must be documented.

4.9 Administration of trial medication

IMP shall be administered/taken and this must documented as described in the approved trial protocol.

General procedures for administering medicinal products to subjects at the hospital shall be followed, unless otherwise specifically described in the protocol.

4.10 Returns

All remaining IMP and/or empty packaging must be returned to the trial centre, unless otherwise specified in the protocol.

Procedures for returning IMP must be described.

If required by the protocol, compliance will be verified by counting the units of the returned IMP.

4.11 Disposal

IMP will be disposed as agreed for the trial. Usually this will be carried out by the pharmacy according to standard procedures, unless agreed otherwise with the coordinating investigator/principal investigator.

Marketed IMP will usually be disposed by the pharmacy or the hospital according to local procedures. No further documentation will be required.

All IMP sent for destruction during the trial must be documented by the investigator or pharmacist and the documentation will be kept in the ISF and sent to supplier if applicable.

4.12 Unblinding / code breaking in blinded trials

Procedures for blinding in blind trials must be agreed before the start of the trial and be in compliance with the SOP Randomisation, blinding and unblinding.

4.13 Recall of IMPs

Recall of IMPs must be documented and a protocol deviation must be written to describe the course of events and what actions were taken to close the case.

4.14 Documentation

All records for IMP and AxMP will be filed in the ISF and a copy will be sent to the sponsor for archiving in the TMF.

5 NON-COMPLIANCE MANAGEMENT

Non-compliance should be handled according to the procedures for handling non-compliance of the individual institution. Protocol deviations should be reported according to the study protocol or the Protocol Deviation Handling Plan.

6 REFERENCES

6.1 External References

- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) in particular chapter 5
- REGULATION (EU) No 536/2014 of The European Parliament and of the Council on clinical trials on medicinal products for human use, chapter IX
- Forskrift om tilvirkning og import av legemidler

6.2 Internal References

- SOP Investigational Medicinal Porduct (IMP) Management at Trial Start
- SOP Randomisation, Blinding and Unblinding
- SOP Protocol Deviation Handling
- Samarbeidsavtale apotek
- Økonomisk avtale apotek

7 ATTACHMENTS

- IMP Handling Checklist
- IMP Requisition Form
- IMP Temperature Log
- IMP Accountabillity Form with kit or ID-number
- IMP Accountability Form Common Stock Unnumbered
- IMP Accountability Form Different Manufacturers
- IMP destruction
- IMP Reconciliation

8 DEFINITIONS

SOP Definitions.

Abbreviation	Term
AxMP	Auxiliary Medicinal Product
CRF	Case Record Form
CRO	Contract Research Organisation
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site FIle
SOP	Standard Operating Procedure

9 CHANGES SINCE LAST VERSION

CT SOP version no 1.0

Main changes from LM SOP no. 3.2. Adapted to the Regulation. Added auxiliary medicinal product.