INVESTIGATIONAL MEDICINAL PRODUCT (IMP) MANAGEMENT AT TRIAL START

1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for documenting and managing investigational medicinal products (IMPs) and auxiliary medicinal product (AxMP), at the start of 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 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.

The coordinating investigator (CI) should ensure that the correct up to date information IMPs and AxMPs is provided to competent authorities and ethics committees and that IMPs and AMPs are handled according to this SOP including:

- Ensure that the IMP is included in the European database for medicinal product (XEVMPD)
- Ensuring that there is a written agreement with an approved manufacturer of IMPs if necessary for e.g blinding of the IMP
- Ensuring that a plan for distribution of IMPs and any AxMP to all sites is in place
- Ensuring that there are written procedures for storage and handling of IMPs and any auxiliary medicinal product at each site

The principal investigator at each site is responsible for managing the IMPs and for keeping records of the use of the IMPs.

4 PROCEDURES

4.1 Requirements for Investigational and Auxiliary Medicinal Product Documentation

Documentation requirements for IMPs include documentation of reference product (active comparator) and placebo, if applicable.

IMP documentation is required by the regulatory authorities, for the assessment of the trial and the overall safety of the products and must be presented when applying for approval of a drug trial to the competent authority (e.g. Norwegian Medicines Agency, SLV) and the Ethics Committee (e.g. Regional Committee for Medical and Health Research Ethics, REK).

The documentation shall provide investigators and other trial personnel with information including the Reference Safety Information (RSI) to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as:

- The dose, dose frequency/interval and methods of administration
- Safety monitoring procedures.

The investigator's brochure (IB) and other documents shall be marked with the version number and date.

When using AxMPs that are not authorised in the participating countries, the same requirements for safety and quality information is required

The documentation which may be required for applications for regulatory and ethics approval for various investigational products is as follows:

4.1.1 Safety information

4.1.1.1 Summary of Product Characteristics (SmPC) (only competent authority)

For IMPs with marketing authorisation the approved Summary of Product Characteristics (SmPC, preparatomtale) can be used instead of investigator's brochure. The SmPC should be in Norwegian or in English.

If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial. This information should be included in the protocol.

For IMPs that are identified in the protocol by its active substance, the coordinating investigator should select one SmPC.

4.1.1.2 Investigator's Brochure

For IMPs without marketing authorisation the sponsor must provide an IB. The investigator's brochure is a compilation of physical, chemical and pharmaceutical properties and formulations, non-clinical and clinical data concerning the IMPs that are relevant to the study of the product(s) in human subjects. This includes data from animal studies, clinical trials, toxicity, pharmacokinetic and pharmacodynamic data, etc.

The IB shall contain a clearly identifiable section called the 'Reference Safety Information' (RSI). The RSI shall contain information on known adverse events and information on what adverse reactions are to be considered as

expected adverse reactions, and on the frequency and nature of those adverse reactions. The IB shall also contain a summary of data and guidance to the investigator.

The requirements for the content in an IB are given in Chapter 7 of ICH GCP and ANNEX I section E of Regulation (EU) No. 536 2014. It is recommended that the attached Investigator's Brochure Checklist and/or Investigator's Brochure Template is used to ensure that the requirements of content are complied with.

The information should be presented in a concise, simple, objective, balanced and non-promotional form.

In a non-commercial trial where a pharmaceutical company owns/manufactures the IMP, CI can ask the company for the IB.

4.1.2 Quality information

If a medicinal product is not authorised in the EEA, CI should ensure that the product is included in the European database for medicinal products (XEVMPD). Preferably, the CI should contact the company developing the product for relevant information about the IMP.

4.1.2.1 Investigational Medicinal Product Dossier (IMPD)

The IMPD gives information related to the quality of any IMP (including reference product and placebo), manufacture and control of the IMP, and data from non-clinical studies and from its clinical use.

For marketed IMPs, it is sufficient to refer to the SmPC.

If the IMP has marketing authorisation in another EU/EEA area or ICH country, or has previously been evaluated in connection with a clinical trial, a simplified IMPD can be submitted. For documentation requirements please refer to ANNEX I, Table 1 of Regulation (EU) No. 536 2014.

When requiring manufacturing of placebo and blinding of IMP, the manufacturer should provide the IMPD to the coordinating investigator. There is a list of approved Norwegian manufacturers on the NorCRIN website. Other EU manufacturers may also be contracted.

If the IMP is not authorised, and does not have a marketing authorisation from a third country that is part of ICH, and is not manufactured in the EU the following documentation shall be submitted:

(a) a copy of the manufacturing authorisation and
(b) certification by the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union, unless there are specific arrangements provided for in mutual recognition agreements between the Union and third countries.

4.1.2.1.1 Documentation of pharmaceutical, chemical, biological quality

For IMPs without marketing authorisation, documentation must be submitted to the competent authority with respect to chemical and pharmaceutical quality. The coordinating investigator should refer to the European Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (revision 2 – January 2022).

4.1.2.1.2 Non-clinical and clinical evidence

For IMPs without marketing authorisation, relevant documentation will be sent appropriate to stage of development, dosage, duration of treatment and patient group. The documentation from non-clinical studies shall be in accordance with applicable European guidelines and ICH guidelines.

For marketed IMPs with used outside the conditions of marketing authorisation, additional non-clinical and clinical data will be sent to Competent Authority to permit assessment of the overall safety of the product(s). It is often sufficient to send the rationale for, or published articles that supports use outside the approved indications. The documentation can be in the protocol or other submitted document. For paediatric trials, it may be necessary to send additional non-clinical and clinical documentation.

4.1.2.1.3 Biological IMPs

Documentation shall be prepared in compliance with the Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.

4.1.3 Summary of requirements

The requirements are summarised in the following table.

IMP:	**Required documentation:**
IMP with marketing authorisation and use in line with SmPC	SmPC (as reference or attachment)
IMP with marketing authorisation outside the conditions of the SmPC	SmPC (as reference or attachment) and non-clinical and clinical data if appropriate (can be included in the protocol)
IMP with marketing authorisation in an ICH country (EU/EEA, USA and Japan) with another indication or different dosage.	SmPC + IMPD (simplified version) including non-clinical / clinical documentation if not described in the protocol.
Blinding of IMP with marketing authorisation in an ICH country (EU/EEA, the US and Japan)	SmPC + IMPD (simplified version) to be provided by the manufacturer
IMP with marketing authorisation in the EU EEA area or ICH country but new pharmaceutical form or strength requiring different manufacturing	SmPC + IMPD (simplified version) to be provided by the manufacturer. Non-clinical / clinical documentation is not necessary
IMP without marketing authorisation	IB + IMPD
Placebo	Manufacturing documentation must be submitted.

4.2 Labelling

The following information shall appear on the outer packaging and on the immediate packaging of

- unauthorised IMPs and unauthorised AxMPs
- studies with blinded label on authorised IMP/AxMPs

(a) information to identify contact persons or persons involved in the clinical trial;
(b) information to identify the clinical trial;
(c) information to identify the medicinal product;

(d) information related to the use of the medicinal product.

The information which is to appear on the outer packaging and immediate packaging shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the clinical trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics.

When using unauthorised IMPs or AxMPs, the manufacturer should ensure the labelling fulfils the requirements.

When using authorised IMPs and AxMPs in studies where there are no blinding of the label, there is in general no additional labelling requirements on the immediate and the outer packaging.

However, depending in the protocol, under specific circumstances to ensure the safety of the subject or the data quality, the following might be required on the immediate and the outer packaging.

(a) name of the main contact;
(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;
(c) 'For clinical trial use only' (Til klinisk utprøving) or similar wording.

Radiophamaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal products shall be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial.

Labelling should be in the local language. If the IMP is only handled by healthcare professionals, local language labelling may not be necessary. In Norway, Danish, Swedish or English is accepted.

Labelling of preparations reconstituted by pharmacies/sites (such as prefilled syringes and infusion bags) only needs to comply with the requirements of the regulations for ordering and release of drugs from the pharmacy. That is, there is no need for trial-specific labelling as long as administered by health care personnel. However, it is recommended to record trial-specific information, to ensure subject safety, and that trial documentation is complete. Pharmacists must be given information about which preparations are part of a clinical trial and patients who are receiving investigational medicinal product.

4.3 Preparation of Documentation

Documentation of IMPs shall be prepared or obtained before an application for approval of the trial is sent to Competent Authority and Ethics Committee.

The coordinating investigator should ensure that appropriate IMP documentation exists, as well as validate and update the documentation of the product(s) if required.

If necessary, external expertise can be obtained from e.g. the pharmaceutical company / manufacturer and/or CRO, to the preparation of the necessary documentation of the product.

4.4 Supply

IMPs with marketing authorisation in countries other than Norway should be imported by the pharmacy or other approved importer. Pharmacies can import directly from the EEA. An approved drug wholesaler or other authorised institution (see list of approved Norwegian on the NorCRIN website) may import from countries outside

the EEA. For not marketed IMPs, competent authority (i.e. SLV for Norway) approval of the product for use in a trial is equivalent to approval exemption.

When using products that are manufactured specifically for a trial, there must be a written GMP technical agreement with an approved manufacturer.

4.5 Randomisation, Blinding and Unblinding

Procedures for randomisation, blinding and unblinding are described in the SOP Randomisation, blinding and unblinding.

4.6 Requests for IMP

Requests for IMP from pharmacies must be made by the investigator. This task cannot be delegated to nurses or other trial staff. Documentation of requests must be filed in the investigator's site file and the sponsor's TMF.

The requisition procedure and any required forms should be agreed before trial start-up. See IMP Requisition Form

4.7 Information for Trial Subjects

Information about the IMPs and possible adverse reactions should be included in the written information given to the trial subjects.

If the IMPs are to be taken home by the subject, information for handling of the IMP should be provided to the subject (see IMP Handling Checklist).

4.8 Revision of documentation

4.8.1 Investigator's Brochure (IB)

Investigator's Brochure will be reviewed at least once a year, and updated earlier if new relevant information emerges.

The annual review shall be documented.

When updating investigator's brochure, the version number and date must be updated. It is advisable to write the previous issue number and date on the updated version.

Significant changes in the investigational product documentation / investigator's brochure will be sent to competent authorities for review. A significant change is, for example:

- new toxicological or pharmacological data
- new interpretation of toxicological
- pharmacological data of relevance for the investigator
- updated benefit / risk assessment or safety profile

Updates that may change the initial risk-benefit assessment of the trial should be submitted to the competent authority.

4.8.2 Summary of product characteristics (SmPC)

To ensure that the latest version of the SmPC is used in the trial, it is recommended that it be checked at least once a year, e.g. in connection with annual reporting, see SOP Safety Reporting. Despite a possible change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the annual reporting period, so that the updated SmPC will be the RSI for the next reporting year.

4.9 Communication of information

The coordinating investigator will send the current written documentation of the investigational product to the principal investigators. All investigators should have the most recently updated version of the documentation available. The delivery and receipt of the documentation should be documented in the study files.

4.10 Filing

All documentation of the IMP is part of the essential documents and will be filed in investigator site file and trial master file. See SOP Study Files.

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 trial protocol or the Protocol Deviation Handling plan.

6 REFERENCES

6.1 External references

- Eudralex volum 10
- ICH Guideline for Good Clinical Practice (GCP) E6 (R2) especially chap. 7
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (revision 2 – January 2022)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (Revision 2 - January 2022)
- European guidelines
- Non clinical guidelines
- ICH guidelines
- Forskrift om rekvirering og utlevering av legemidler fra apotek
- REGULATION (EU) No 536/2014 of The European Parliament and of the Council on clinical trials on medicinal products for human use, chapter IX

6.2 Internal references

- SOP Randomisation, blinding and unblinding
- SOP Application Process, Approvals and Start-up
- SOP Study Files
- SOP Protocol Deviation Handling

- SOP Safety Reporting

7 ATTACHMENTS

- Investigator's Brochure (IB) checklist
- Investigator's Brochure (IB) Template
- 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 Reconciliation
- IMP Destruction
- IMP Handling Checklist

8 DEFINITIONS

SOP Definitions.

Abbreviation	Term
AxMP	Auxiliary Medicinal Product
CI	Coordinating Investigator
CRO	Contract Research Organisation
CTS	Clinical Template Suite
EEA	European Economic Area
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
RSI	Reference Safety Information
SmPC	Summary of product characteristics

SOP	Standard Operating Procedure
XEVMPD	European database for medicinal product

9 CHANGES SINCE LAST VERSION

CT SOP version no 1.0.

Merging of LM SOP no. 2.07 and LM SOP 2.13. Adapted to the clinical trial regulation no 536/2014 including auxiliary medicinal products and low-intervention trials. Change of labelling requirements for authorised IMP/ AxMPs.