1 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for clinical trials of advanced therapy investigational medicinal products (ATIMP).

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

2 SCOPE

This SOP is valid for all clinical trials of ATIMPs sponsored by clinicians in Norwegian hospitals which are part of NorCRIN.

This SOP provides procedures that are required in addition to the principles described other NorCRIN SOPs, which are necessary for advanced therapy medicinal products.

If the sponsor is external, e.g. a pharmaceutical company, the sponsor's SOPs will be used, provided that these are in line with national and international laws, regulations and ICH GCP.

Products of animal origin are not included in the scope of this SOP. However, if an animal product is used then the requirements for animal products stated in EU Directive 2004/23/EC, should be followed.

3 RESPONSIBILITY

The sponsor has overall responsibility for ensuring that clinical trials of advanced therapy medicinal products are carried out in compliance with Regulation (EC) No 1394/2007, other applicable regulations and this SOP.

The sponsor's responsibilities shall be described in the governing documents (quality system) of the individual health facility / the individual institution. Tasks can be delegated. The delegation of tasks shall be documented.

The national coordinating investigator (for multi-centre studies) and / or the principal investigator (for single-centre studies) are responsible for ensuring that clinical trials of ATIMPs are conducted in compliance with ICH GCP, the European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal products, and this SOP.

Where multiple parties are involved the sponsor will ensure that the contractual agreements define the role of each and that specific procedures are defined to ensure that the integrity of the traceability of the ATIMP.

4 PROCEDURES

4.1 Overarching Principles

The sponsor should ensure that the over-arching principles laid down in the EMA detailed guidelines on good clinical practice specific to advanced therapy medicinal products are followed. Specifically with regard to traceability of ATIMP and ensuring that records contain sufficient detail to link donors and subjects. The sponsor should also ensure that appropriate risk analysis is performed and documented in the protocol, investigators brochure or elsewhere.

4.2 Communication with the EMA Committee for Advanced Therapies

The NCI/PI should consider contacting the EMA committee for advanced therapies:

- If there is any doubt about the classification of a treatment as an advance therapy
- For scientific evaluation and certification

The first step is to submit a pre-submission request form which can be downloaded from the EMA web site.

4.2.1 Classification

If there is any doubt about whether or not a treatment is an advanced therapy, as defined by the Regulation (EC) No 1394/2007, the NCI/PI should consider requesting a scientific recommendation from the EMA with a view to determining whether the product falls, on scientific grounds, within the definition of an advanced therapy medicinal product.

The information which should be provided includes:

- Description of active substance
- Description of the finished product
- Mechanism of action and proposed use
- Summary of the status of the development of the product

The classification request form can be which can be downloaded from the EMA web site.

4.2.2 Scientific evaluation and certification

The NCI/PI should consider submitting all relevant quality and, where available, non-clinical data to the EMA for scientific evaluation and certification of a new ATIMP.

Information which could be submitted with the request form includes but is not limited to:

- The stage of development and in particular the stage of any study in pre-clinical or clinical setting whether planned, ongoing or completed
- Starting and raw materials
- Manufacturing process of the active substance(s)
- Data on characterisation of the active substance(s) (limited to the data necessary to adequately describe the active substance(s)),
- Description and composition of the finished medicinal product

- Primary pharmacodynamic data supporting the rationale for the proposed therapeutic use
- Data from at least one toxicity study
- Data from non-clinical pharmacology studies (proof-of-concept studies)

Further information and the ATMP certification form can be found on the EMA web site.

4.3 Traceability

The sponsor will ensure that the use of each ATIMP is traceable. Records will be kept which document each individual product so as to ensure traceability from sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition.

The traceability procedures to ensure full traceability from the donor to the recipient and the documentation process, should be described in the clinical trial protocol.

An anonymous coding system will be used to ensure traceability is consistent with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

4.4 Risk Analysis

The sponsor will carry out ongoing risk analysis, based on existing knowledge of the type of product and its intended use and ensure that all investigators involved in a clinical trial with that ATIMP are informed by including that information in the investigator's brochure.

The sponsor will also ensure that the risks identified in the risk analysis are described in the patient informed consent documentation.

If necessary, the sponsor will consult the national competent authorities for biosafety for their advice on the risks associated with the ATIMP.

4.5 Donation, Procurement and Testing of ATIMPs

If the sponsor is responsible for the requesting donation, procurement and testing of human cells and tissues used for the manufacturing of an ATIMP they will ensure that these procedures are carried out in accordance with the current regulations and applicable GMP annexes (i.e. Annex 2 and Annex 13).

4.6 Protocol

In addition to the usually requirements for a clinical trial protocol, the sponsor will ensure that the protocol contains adequate information about variabilities in the nature of ATIMPs and the diseases for which they are used.

If there is any variability inherent in the use of the ATIMP then the protocol should define the appropriate degree of flexibility that may be used for the handling of any variability, for example, the acceptable range of cell numbers and cell viability at the time of administration to subjects.

Where an ATIMP contains human cells or tissues, the protocol should contain the following:

- Confirmation that the donation, procurement and testing of the human tissues and cells are in conformity with the relevant regulations, (i.e. Article 3 of the Regulation 1394/2007)
- Description of the donor type and whether the donation is part of the trial process
- The criteria used to confirm the suitability of the donated material.

Where an ATIMP incorporates a medical device the protocol should contain:

- A brief overview of the characteristics, performance and purpose of the device
- Confirmation that this product is in conformity with essential requirements of the appropriate device regulations (Directive 93/42/EEC or Directive 90/385/EEC for active implantable devices)
- The rationale for combination of the ATIMP and medical device to aid understanding of the effect of each individually and in combination

The protocol should also include information on the follow up strategy (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment.

4.7 Informed consent

When obtaining consent from donors and recipients, the investigator should ensure that sufficient time is allowed. In addition to the usual requirements for consent the investigator must ensure that clear and sufficient information is given to both the donor and recipient, including, but not be limited to information about the:

- Source
- Implications for the donor in the event of identification of known or novel infectious or genetic disease markers and the possibility to waive the requirement for follow-up information.
- Testing and screening procedures
- Requirement for traceability and its implications
- Time for which the consent is valid
- Retention of samples
- Storage or discarding of surplus materials

The investigator must also ensure that adequate training has been provided to anyone who gives information and obtains consent.

4.8 Adverse Event Reporting

The sponsor should ensure that new events related to the conduct of the trial or the development of the ATIMP and likely to affect the safety of the subjects should be reported according to the existing timelines for expedited reporting.

This includes:

- Serious adverse events which could be associated with the trial procedures and which could require modification of the conduct of the trial
- Significant hazard to the subject population.

The process for reporting of adverse events should be outlined clearly in the clinical trial protocol. The following safety issues should be addressed:

- Adverse events related to the product application process (surgical or other)
- Suspected or confirmed cases of infection
- Unexpected reactions (e.g. hypersensitivity, immunological, toxic or other as consequence of a change in the construction or function of the viral vector (e.g. generation of replication competent virus)
- Adverse events related to product failure (including lack of efficacy)
- Adverse events related to mandatory concomitant medication (e.g. immunosuppression)
- Adverse events related to medical devices which form part of the product or are used for application of the product

4.9 Follow-up

The sponsor should ensure adequate follow up procedures including but not limited to:

- Follow up for the protection of the subject i.e. clinical follow up;
- Follow up for the purpose of collection of specific data (which might not involve all subjects) i.e. safety follow up and efficacy follow up.

All subjects participating in a clinical trial with an ATIMP should receive from the investigator an alert card, which has been previously agreed by the sponsor and approved by the Ethics Committee, containing as minimum the name of the subject, the investigator contact number and information regarding the medical treatment received.

4.10 Documentation and Archiving

The sponsor will file and archive all the following required essential documentation (listed in the EMA detailed guidelines on good clinical practice specific to advanced therapy medicinal products) archived and retained for 30 years after the expiry date of the product:

- Identification of the tissue establishment/animal facility/any intermediaries if applicable
- Type of tissue and cell/product (basic nomenclature)
- Pool number (if applicable)
- Split number (if applicable)
- Tissue/cell status (i.e. quarantined, suitable for use etc.)
- ATIMP identification
    - Tissue/cell status (i.e. quarantined, suitable for use etc.)
    - Description and origin of the products, processing steps applied materials and
    - additives coming into contact with tissues and cells and having an effect on their
    - quality and/or safety.
    - Identification of the sponsor, contract research organization or investigator/institution to whom the product is supplied
    - Product name/code
    - Pharmaceutical form, route of administration, quantity of dosage units and strength
    - Batch and/or code number

  - Trial reference code
  - Trial subject identification number
  - Expiry date
  - Date of distribution/disposal
  - Release of the finished product by the Qualified Person

- Shipping Records for IMP
- Certificate of analysis of the IMP
- Treatment allocation and decoding documentation
- IMP accountability at the site, including final disposition of both used and unused product.
- Identification of the manufacturing site
- Identification of the investigator/institution that used the ATIMP
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject code
- Expiry date
- Date of application

The investigator will ensure that the following traceability records are archived and retained for 30 years after the expiry date of the product:

- Shipping Records for IMP
- Treatment allocation and decoding documentation
- IMP accountability at the site, including final disposition of both used and unused product
- Identification of the manufacturing site
- Identification of the investigator/institution that used the ATIMP
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject code
- Expiry / retest date
- Date of administration
- Subject identification code list

5 NON-CONFORMANCE MANAGEMENT

All non-compliance should be handled according to the procedures for handling non-compliance of the individual health facility / institution.

6 REFERENCES

6.1 EXTERNAL REFERENCES

- Health research the law § § 7, 29 and 37.
- Integrated Addendum To ICH E6(R2): Guideline for Good Clinical Practice
- Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
- Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 2: Manufacture of Biological Medicinal Products for Human Use
- Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13: Investigational Medicinal Products
- Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Directive 2002/98/EC of the European Parliament and of the Council on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC
- Proposal for Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009
- Council Directive 93/42/EEC concerning medical devices
- Council Directive 90/385/EEC concerning active implantable medical devices

6.2 INTERNAL REFERENCES

7 ATTACHMENTS

8 DEFINITIONS

- Definitions

9 CHANGES SINCE LAST VERSION

Version 3.0. New SOP.