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GUIDELINES

on Good Clinical Practice for Advanced Therapy Medicinal Products

Table of contents

This document is intended for consultation purposes and it does not contain the official position of the European Commission.

1. Introduction

1.1. Scope

Compliance with good clinical practice ("GCP") is mandatory for clinical trials that are conducted in the EU.[1] Article 4 of Regulation (EC) No 1394/2007[2] mandates the Commission to draw up guidelines on good clinical practice specific to advanced therapy medicinal products ("ATMPs").

These Guidelines develop the GCP requirements that are specific to clinical trials conducted with ATMPs. These Guidelines are to be read in conjunction with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on good clinical practice,[3] which are also applicable to ATMPs. To the extent that there is a difference in the requirements, the content of these Guidelines prevails.

These Guidelines do not apply to clinical trials with medicinal products other than ATMPs.

1.2. General context

ATMPs are complex and innovative products that may pose specific challenges to the design and conduct of clinical trials. For example, manufacturing constraints and the short shelf-life of the product may require the implementation of tight controls on logistical arrangements to administer the product. Likewise, the mode of application may render very difficult the use of placebo controls and/or may require specific training. Additionally, the long-term effects of the product may require specific arrangements for long-term follow-up of the subjects. Moreover, it is recognised that it may not always be feasible to generate relevant non-clinical data before the product is tested in humans.

While the general principles of GCP set out in ICH Guidelines are applicable to clinical trials with ATMPs, in some cases, it may be necessary to adapt those to the specific characteristics of ATMPs (*e.g.* regarding retention of samples). The implementation of additional measures may also be necessary (*e.g.* traceability requirements for ATMPs that contain cells or tissues of human

[1] Article 47 of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p. 1). Until the Regulation enters into force, Directive 2001/20/EC applies (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p.34.)

[2] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L324, 10.12.2007, p.121).

[3] ICH E6 Good Clinical Practice Guideline adopted by CHMP as EMA/CHMP/ICH/135/1995, as updated.

origin, follow-up of patients after end of the clinical trial, training on upstream intervention of subjects and/or administration procedures).

Clinical trials with ATMPs performed in the EU are governed by Regulation (EU) No 536/2014 on clinical trials and should comply with the requirements provided for therein, including regarding the content of the application dossier. While some ATMP specific considerations relevant to ATMPs are explained in this Guideline, it is stressed that these are non-exhaustive and that the specific content of the cover letter, Protocol, Investigators Brochure ("IB"), and Investigators Medicinal Product Dossier ("IMPD") is laid down in the Regulation (EU) No 536/2014.

2. Clinical Trial Design

The design of clinical trials with ATMPs should take into account the specific characteristics of these medicinal products, as well as the potential risks to subjects, investigator's team and others (*e.g.* offspring, close contacts). In particular, the following should be taken into consideration:

(i) ***Study population***: The choice of study population should take into consideration aspects related to the risks and benefits for the subjects, as well as the ability to provide interpretable data. Examples of considerations related to the risks and benefits for the subjects include the following:

- The relation of the anticipated benefits to the potential risks of the ATMP should be at least as favourable as existing alternative approaches. Particular consideration should be paid in cases where the exposure of the clinical trial subject to the ATMP is long-lasting and/or irreversible.

- When the clinical trial population involves paediatric subjects or foetuses (in utero treatment or treating of the mother bearing the child), consideration should be given to the implementation of additional safeguards, which should be adapted to the specific characteristics of the product, the treated disease and the developmental stage of the population. While it is generally advisable to stagger trials by age, it is acknowledged that treatment of the patient at a very young age may be necessary without a staggered approach (*e.g.* severe genetic diseases where irreparable damage occurs early on and/or where the medicinal product is only expected to benefit patients in early stages of disease, or in case of life threatening conditions).

  It is expected that prior studies in adults are performed unless the condition is life-threatening, or the sponsor justifies why these are unethical, not feasible or not relevant (*e.g.* in cases of diseases exclusively affecting paediatric patients).

- For populations that might ultimately be amenable to transplantation, sponsors should consider whether exposure to the ATMP would cause sensitisation and potentially compromise future transplant success. Likewise, in case of gene therapy medicinal products, the impact of pre-existing immunity should be duly considered.

- The health condition of the clinical trial subject should be duly considered in the design of the trial, in particular in cases of life-threatening diseases where there is a risk that the trial subjects may not survive until the administration of the investigational medicinal product (*e.g.* long period required for manufacturing, patient in too critical condition to survive leukapheresis or preconditioning regime).

(ii) ***Cohorts:*** The cohort size number usually depends on disease prevalence and manufacturing capacity. Having regard to these constraints, the sponsor should select a cohort size feasible and adequate to meet study objectives.

Depending on the degree of safety concern, staggered treatment of individual subjects within each new cohort and between cohorts should be considered in early phase clinical trials, as appropriate.

(iii) ***Comparators***: If an active comparator is not available, comparison with best standard of care can be considered. An intra-subject control may also be considered when appropriately justified. For example, intra-subject control may be suitable to investigate pre and post treatment biomarker levels for an established surrogate (*e.g.* in trials involving subjects with Haemophilia A and B, subjects can act as their own controls during the pre-treatment phase of the clinical trial).

(iv) ***Blinding***: While comparison to standard of care or no treatment sometimes makes double-blinding for the investigator(s) or the surgical investigator team unfeasible or unethical, blinding for subjects should be maintained where possible. Additionally, when the investigator is unblinded, outcome assessment by (a) blinded observer(s) should be considered.

(v) ***Placebo***: The use of placebo should be scientifically and ethically justified. When invasive procedures are required to administer the ATMP or for the collection/extraction of the cells/tissues, control groups receiving placebo only should not be subjected to a procedure if it presents more than minimal risk and minimal burden. The risk posed by the procedure should be duly explained in the Protocol.

(***vi)*** ***Dosing***: Early phase clinical trials should attempt to define the dose range to be used in the pivotal trial. It is acknowledged that the determination of the dose may be challenging and sponsor should duly consider aspects such as:

- The cells that are active may be difficult to identify and may be different from those causing adverse drug reactions (ADRs).
- In some instances the ATMP may contain inactive particles (*e.g.* empty capsids or virus like particles) which may impact transduction efficiency and potency.
- For some autologous products or patient specific allogeneic donor products, the cell numbers may vary for each dose due to the intrinsic variability of the starting materials.

- Therapeutic effect may be linked to engraftment or transduction efficiency.

Aspects of dosing and repeatability of treatment should be duly considered based on the specific characteristics of the product. For example, where the ATMP is expected to have long-term effects, dose escalation and repeated dosing should be considered with a view to improve the control of toxicity risks to the subject.

However, a dose escalation strategy may not be necessary (*e.g.* if there are no toxicity concerns associated with the investigational ATMP) or appropriate (*e.g.* when it is not possible to re-administer the product or when the re-administration involves the additional risk of a surgical procedure). In such cases, the exploratory dose chosen should aim to be a therapeutic dose for the subject, taking the observed non-clinical safety margin into consideration.

A rationale for a dose definition based on published literature data requires a thorough analysis of the comparability between products, including on aspects relating to starting material and manufacturing process, as well as the characteristics of patient populations treated.

A description and justification of the dosage should always be provided in the Protocol. Additionally, in case of ATMPs with complex dosing regimens, the IB should contain adequate explanations for the rationale to ensure an adequate level of understanding and compliance by the investigator and those involved in the clinical trial.

(vii) End of the trial: The definition of "end of the trial" should be clear and unambiguous. Due to the mode of action, novelty and scientific uncertainties that may exist in connection with ATMPs, there might be a need for patients to be on long-term follow-up after treatment. In these cases, it becomes especially important to define clearly the event that marks the end of the trial and to explain in the Protocol how follow-up activities will be performed after the end of the trial (*e.g.* via an interventional clinical trial or non-interventional follow-up).

3. Non-clinical studies

Non-clinical studies should be carried out with the most appropriate and relevant *in vivo* and *in vitro* models. However, it is acknowledged that animal models may not always be capable of providing reliable information on the safety of the treatment due to the problems of incompatibility between humans and animal species. In contrast, testing animal cells in animal models does not permit to predict the safety profile of the actual medicinal product either. It follows that the ability of non-clinical data to guide various aspects of the design of the early-phase clinical trial should be assessed case by case.

Likewise, in some cases it will not be feasible to conduct traditional non-clinical pharmacokinetic (PK) or dose finding studies; the extrapolation of a potentially safe and possibly bioactive starting clinical dose from animal data will be influenced by species specificity and immunogenicity, *etc*.

The rationale for the non-clinical development should be discussed and justified, including in cases where the sponsor considers that non-clinical studies are not feasible.

Comprehensive information about the non-clinical development should be provided in the IB. A summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial should be provided in the Protocol. The IMPD can cross-refer to the information contained in the IB.

4. Quality of the investigational ATMPs

4.1. General considerations

Investigational ATMPs should comply with the Commission Guidelines C(2017) 7694 of 22 November 2017 on Good Manufacturing Practice for Advanced Therapy Medicinal Products.[4]

The impact of the variability of donor or patient based starting material should be taken into consideration when defining release specifications for cell-based ATMPs (*e.g.* cell numbers/range of cell numbers, transduction efficiency). In the autologous setting, consideration should be given to how the disease status of the patient impacts on the quality of the starting material and potential variability of the final drug product.

Storage, transport and handling conditions have the potential to negatively impact the quality of ATMPs. The sponsor should provide the investigator with detailed instructions for the handling and storage of investigational product(s) in the clinical trial site.

Where the ATMP requires controlled temperature conditions during transport and/or storage prior to administration, the sponsor should ensure there is a temperature monitor/ log data and/ or confirmation that required conditions have been met.

In case of investigational ATMPs with short shelf life, timelines should be clearly documented in the trial records in relation to time from manufacture to time of administration to subject.

In case of complex handling processes, the sponsor should provide the investigator with adequate training.

4.2. Tissues and cells of human origin

Where an ATMP contains cells or tissues of human origin, the IMPD should contain:

- the confirmation that the donation, procurement and testing of the cells and tissues used as starting materials are in accordance with Directive 2004/23/EC[5] or Directive 2002/98/EC,[6] and

[4] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf
[5] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L102, 7.4.2004,p.48).

- the confirmation that a traceability system is in place that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, up to the administration of the investigational product to the clinical trial subject.[7]

4.3. Medical devices

Devices may be used in the context of ATMPs in different ways. They may be part of the active substance or the formulation ("combined ATMP"), function as container closure system, or be specifically required for the application/administration of the ATMP.

Where an ATMP incorporates a medical device ("combined ATMP" and medical devices that are otherwise an integral part of the investigational ATMP), the IMPD should contain:

- information on the characteristics, performance and intended use of the device; and
- information whether the medical device part(s) comply with the relevant general safety and performance requirements provided for under Regulation (EU) No 2017/745 on medical devices.[8] When this is not the case (*e.g.* the medical devices used in an investigational combined ATMP are in an investigational phase as well), a justification should be provided as to the suitability of the medical device for the intended use, having due consideration to the relevant general safety and performance requirements.

Where applicable, the cover letter should contain a list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use. In addition, the Protocol should contain summary information on the characteristics, performance and intended use of the device, as well as its regulatory status.

4.4. Reconstitution

When the investigational ATMP requires reconstitution before it is administered to the subject, the sponsor should ensure that the detailed instructions of the reconstitution process (as validated by the manufacturer of the product) are transmitted to the sites where the product is going to be administered. The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product (*e.g.* it is generally expected that, when the reconstitution involves thawing, the rate of temperature change during thawing is described.)

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[6] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 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 (OJ L 33, 8.2.2003, p. 30).

[7] The system should be complementary to and compatible with the traceability requirements under Directive 2004/23/EC or Directive 2002/98/EC.

[8] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (OJ L 117, 5.5.2017, p. 1) will apply after a transitional period and entry into force 26 May 2020, until then Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169, 12.7.1993, p. 1) applies.

Likewise, when the reconstitution requires the use of solvents and/or other materials these should be specified or, as appropriate, provided by the sponsor.

The reconstitution should be described in the IB. It is acceptable that the detailed instructions are laid down in a separate document available at the site (*e.g.* handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.

Where appropriate (*i.e.* in the case of complex reconstitution procedure), training should be provided to those involved in the reconstitution process.

5. Safe conduct of the clinical trial

5.1. Information on the product

The IB should provide comprehensive information on the risks of the product (based on existing knowledge), including risks associated with the administration procedure and/or upstream interventions on subjects, and information on short and long-term safety issues particular to ATMPs such as infections, immunogenicity/immunosuppression and malignant transformation.

Information should also be provided on the potential impact of previous or concomitant treatments (*e.g.* in case of gene therapy medicinal products, risks associated with prior infection /vaccination with related viruses), as well as the potential consequences of the investigational medicinal product for the patient in case he/she requires further treatments for the targeted disease (*e.g.* an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction). Where appropriate, the risk of treatment failure should also be addressed.

The IB should be updated with information on emerging issues, including changes to the reference safety information as appropriate. A substantial modification application should be submitted to the relevant competent authorities for any change that is likely to have a substantial impact on the safety or rights of the subjects, or on the reliability and robustness of the data generated in the clinical trial.

5.2. Handling of the investigational ATMP

Detailed information should be provided in the IB on the product handling, containment and disposal. It is acceptable that detailed instructions are laid down in a separate document available at the site (*e.g.* handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.

The level of information should be commensurate to the risks. For example, in case of ATMPs that contain infectious biological material, it is expected that detailed instructions for handling and disposal are provided. In case the ATMP includes a bacterial or viral vector with the potential for shedding, the risks and precautionary measures should be clearly communicated to the subject and/or, as appropriate, to caregivers.

Where necessary, information on risk minimisation measures to protect health care professionals that are involved in the handling of the medicinal product should also be provided.

5.3. Risk-minimisation measures

Where appropriate, information should be provided in the Protocol and the IB on the measures that should be put in place to protect clinical trial subjects from identified risks. The following are some non-exhaustive examples:

- if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be described, including liaison with clinical staff where out of specification test results (for sterility) are obtained after the release of the product.

- if there is a risk that a subject that has received an investigational ATMP develops cytokine release syndrome, the investigator should be informed about measures that should be in place before treating the patient (*e.g.* availability of IL-6 inhibitors).

6. Upstream interventions on subjects and administration procedures

6.1. Upstream interventions on subjects

In an autologous setting, the patient undergoes a medical intervention to extract cells/tissues prior to the manufacture and administration of the investigational medicinal product. The process of taking biopsies/extracting cells may entail risks to the subject and may also have an impact on the quality and safety of the product. Therefore, when such processes deviate from standard clinical practice (*e.g.* the collection of cells is done through leukapheresis but the conduct of the leukapheresis requires specific adaptation), they should be clearly explained. The level of documentation should be adapted to the complexity and the novelty of the procedure.

It is acceptable that detailed instructions are laid down in a separate document available at the site, provided that this document is also submitted as part of the application *(e.g.* attached as Annex to the Protocol or IB.)

6.2. Administration procedures

When the administration process deviates from standard clinical practice, the detailed instructions for administration should be described in the Protocol or IB. It is acceptable that detailed instructions are laid down in a separate document available at the site, provided this document is also submitted as part of the application *(e.g.* attached as Annex to the Protocol or IB.)

The level of documentation should take into account the complexity and novelty of the procedure. Where appropriate (*i.e.* in the case of complex administration procedure), training should be provided to those involved in the process.

The presence of the sponsor (or a representative thereof) during the administration of the ATMP to the clinical trial subject or in any upstream collection procedure is only acceptable if it is duly justified. If such presence is envisaged before the start of the clinical trial, this should be

explained in the informed consent. If, exceptionally, the presence of the sponsor (or a representative thereof) has not been foreseen from the outset of the clinical trial but it is justified for reasons related to the protection of the clinical trial subjects or to detect and prevent errors in the extraction of cells/tissues and/or administration, the clinical trial subject should be informed *a posteriori*. As appropriate and in connection with the enrolment of future patients, the sponsor should submit an amendment to the protocol and an update to the informed consent.

7. Traceability

The use of each investigational medicinal product should be traceable. The individual product should be traceable from delivery to the clinical trial site up to the administration to the clinical trial subject.

In addition, when the investigational product is an ATMP that contains cells or tissues of human origin, the traceability from the recipient of the product to the donor of the cells or tissues should be ensured. The traceability system should be bidirectional (from donor to subject and from subject to donor) and data should be kept for 30 years after the expiry date of the product, unless a longer time period is required in the clinical trial authorisation.[9]

The sponsor should ensure that the manufacturer of the investigational ATMP has set up a system that enables the bidirectional tracking of cells/tissues contained in ATMPs, in accordance with the requirements laid down in the Guidelines on Good Manufacturing Practice for ATMPs. The sponsor should also provide the investigator with detailed instructions to ensure traceability of the cells/tissues contained in the investigational ATMP. The role and responsibilities of the manufacturer, the sponsor and the investigator in the implementation of the traceability system should be clearly documented, as well as the location of the traceability records.

Traceability data should be kept also in cases where the clinical trial is suspended or prematurely ended. If the product development is transferred to another entity, the traceability data should be transferred to the new owner, who should assume also the traceability obligations. In the case when the sponsor ceases to exist, the custody of the traceability data should be discussed with the competent authorities that authorised the clinical trial in the EU.[10]

The requirements for traceability should be ensured respecting the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.[11] Therefore the system should allow full traceability from the donor to the recipient through an anonymous coding system.

[9] Cells and tissues used as starting materials for ATMPs should be traceable from the point of donation. The requirements applied at donation and procurement centres to ensure traceability of the cells/tissues are, however, outside the scope of this Guideline.

[10] After Regulation (EC) no 536/2014 becomes applicable, the sponsor should discuss the custody of traceability data with the reference Member State.

[11] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (OJ L 119, 4.5.2016, p. 1).

8. Retention of samples

Under general GCP principles, the sponsor should maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications. However, in the case of ATMPs, it is acknowledged that the retention of samples of the investigational medicinal product may be challenging due to the scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep samples of the investigational medicinal product in the case of autologous ATMPs and certain allogeneic ATMPs (matched donor scenario). In other cases where the scarcity of the materials is also a concern, the sampling strategy may be adapted provided that this is duly justified.

The retention period should be adjusted to the stability and shelf-life of the product and, therefore, shorter periods may be justified for ATMPs. In cases of short shelf-life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf-life (such as cryopreservation) is representative for the intended purpose.

In cases where a sample of the investigational product cannot be kept, photographs or copies of the label should be retained.

9. Protection of clinical trial subjects

9.1. Informed consent

Subjects that participate in clinical trials with ATMPs should receive comprehensive information on the expected benefits and risks of the product, including the risk of treatment failure and effects of the treatment on the future use of other therapies for the diagnosis or treatment of the disease, as well as risks associated with upstream interventions or the administration procedure.

Where applicable, the subject should also be informed of the irreversible nature of the ATMP, and of risks to close contacts and off-springs, or if the treatment could compromise future pregnancies.

The need for long-term follow-up and/or arrangements for remote follow-up should be clearly communicated, where applicable, and subject commitment should be sought (also in respect of any eventual collection of samples).

The subject should be informed when the sponsor (or a representative thereof) is present during the upstream collection of cells/tissues and/or administration procedure as explained in Section 6.

9.2. Long-term follow-up

9.2.1. General principles

The safety profile for some investigational ATMPs may not be fully elucidated, in particular with respect to long-term effects. The duration of the biological activity of a given ATMP should be taken into consideration when determining the need of subject follow-up. Where applicable, the establishment of a scheme for long-term follow-up should be described in the Protocol (or an associated document) and it should be clearly specified -where appropriate- which follow-up

activities take place after the end of the clinical trial (*e.g.* interventional clinical trial or non-interventional follow-up).

The length of the observation period should be based on a risk-assessment having regard to all information available to the sponsor, including –as appropriate- factors such as the observed duration of vector persistence, ability to integrate, potential for latent persistence and reactivation, duration of transgene expression, as well as non-clinical data and/or experience with relevant products. In assessing whether bibliographic data from other products is relevant, account has to be taken not only of the similarity of the product, including the transgene expressed and the administration route. If the risk of delayed adverse events is low, long-term follow-up is not required. Where long-term follow-up is necessary, it is recommended that the sponsor considers discussing the duration of the monitoring scheme with the concerned national competent authority.[12]

When clinical trial subjects should be followed after the investigational ATMP has been granted a marketing authorisation, it is recommended that the monitoring of the clinical trial subjects is integrated with the mechanisms foreseen in the marketing authorisation for the follow-up of subjects treated with the authorised product.

9.2.2. Remote follow-up

In some cases, the follow-up of clinical trial subjects may be challenging, for example, when patients enrol to participate in a clinical trial that is conducted far away from their place of residence and they are not willing to return to the investigator site for the follow-up.

Detailed arrangements for the remote conduct of follow-up activities should be explained in the Protocol or an associated document. If the sponsor plans to gather follow-up data from sources other than visits of the subject to the clinical trial site, the process of gathering data should be clearly explained (*e.g.* use of digital tools or phone calls, visits of the clinical trial subject to a local physician).

The sponsor is responsible to ensure that a robust system for the collection of adverse events is in place and he/she should explain in the Protocol (or associated document) how the quality of the data collected will be ensured. Measures that could be considered include the training of local physicians, establishment of SOPs for use by local physicians/nurses/healthcare professionals, internal audits, ensuring the preservation of samples taken from subjects in case retesting becomes necessary, *etc.*

The responsibilities of each of the parties involved (*e.g.* sponsor, investigator, local physician, nurses, other healthcare professionals involved) should be laid down in writing. All data collected should be centralised and be available for inspection at the clinical trial site.

9.2.3. Premature end or termination

[12] After Regulation (EC) no 536/2014 becomes applicable, the sponsor should discuss the long-term follow up with the reference Member State.

If a subject stops participation in the trial or does not want to continue administration of the investigational medicinal product (in a repeated dosing scenario), the investigator should identify if the subject wants to withdraw completely from the trial and any follow-up, or if the subject accepts follow-up and the consent for this remains. The subject's decision and the follow-up activities should be appropriately documented.

When long-term follow-up is foreseen in the Protocol, monitoring of subjects treated should be ensured also in cases of early termination of the clinical trials. The sponsor should also ensure that there is a process in place for follow-up of the subjects treated with the product in cases where the product development is discontinued or the (former) sponsor ceases to exist, for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial.

If the product development is transferred to another entity, responsibility for the follow-up obligations of treated patients should be transferred to the new owner.

9.2.4. Patient alert cards

Depending on the characteristics of the ATMP, patient alert cards may need to be provided to subjects participating in ATMP trials, with the objective of informing treating physicians about the product used with a view to facilitate medical care of the patient in case of an emergency and to facilitate reporting of adverse events.

Alert cards should contain -as a minimum- the name of the subject, an investigator contact number and information regarding the medical treatment received.

9.3. Administration of out of specification products

As explained in Section 4.1, the variability in the nature of the ATMPs should be taken into account when defining the release specifications.

Exceptionally, in cases where the release specifications as set out in the investigational medicinal product dossier are not met but the administration of the cells/tissues that are contained in a cell/tissue based ATMP is necessary to avoid an immediate significant hazard to the subject, taking into account the alternative options for the subject and the consequences of not receiving the cells/tissues contained in the product, the supply of the product to the investigator is justified.

When the request of the investigator is received, the manufacturer/sponsor should provide him/her with its evaluation of the risks. Records of the investigator's request should be kept in the manufacturing site. The relevant competent authority should be notified swiftly after an out of specification batch has been administered to a subject.

10. Safety Reporting

Where appropriate, reporting forms and data capture systems (serious adverse events forms, case report forms for recording of adverse events) should be adapted to reflect a differentiated causality assessment for each component of the ATMP (*e.g.* the cell-based part and the medical

device part in the case of combined ATMPs), the application process and, where applicable, any required concomitant medication.

While the safety concerns are closely linked to the specific characteristics of the ATMP, the following safety issues should be specifically considered (non-exhaustive list):

- adverse events possibly related to the product administration process (surgical procedures; or other),
- adverse events possibly related to medical devices that form part of the product or are used for application of the product,
- adverse events possibly due to unexpected reactions such as hypersensitivity, immunological, toxic; or migration of cells from the target site and ectopic tissue formation,
- adverse events possibly related to product failure (including lack of efficacy), and
- adverse events possibly related to mandatory concomitant medication (e.g. immunosuppression).

The sponsor should provide information and, as appropriate, training to the investigator on any additional Protocol and/or product specific requirements for the reporting of adverse events.

In cases where long-term follow-up of trial subjects is foreseen, aspects related to the reporting of adverse events during the follow-up period should be clearly specified as part of the long-term follow-up arrangements.

11. Monitoring

The sponsor should adequately monitor the conduct of the clinical trial as provided for under Article 48 of the Regulation (EC) No 536/2014 and the ICH guidelines on good clinical practice.

In the case of ATMPs that contain cells or tissues of human origin, monitoring activities should also cover compliance with the traceability requirements.

Where applicable, compliance with the arrangements for long-term follow-up to subjects (as described in the Protocol) should also be verified.

If the investigational medicinal product accountability records are kept at the clinical trial site, an adaptation of the form to the study specific requirements may be required. It is therefore recommended that these records are designed to reflect the specificities of the ATMPs (*e.g.* blinding issues, preparation/reconstitution steps between receipt and administration of the ATMP).