Consultation Document

Good Clinical Practice for Advanced Therapy Medicinal Products

The sole purpose of this consultation is to collect relevant evidence and information from stakeholders to help the Commission develop its thinking in this area.

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

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1. Introduction

1.1 Scope

Compliance with good clinical practice ("GCP") is mandatory for clinical trials that are conducted in the EU. Article 4 of Regulation (EC) No 1394/2007[1] 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 that are conducted with ATMPs. These Guidelines are to be read in conjunction with the ICH guidelines[2] on good clinical practice, which are also applicable to ATMPs. To the extent that there is a difference in the requirements, the content of these Guidelines should prevail.

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

1.2 General principles

Advanced Therapy Medicinal Products (ATMP) are complex and innovative products which may pose specific challenges to the design and conduct of the 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 preclinical data before the product is tested in humans.

While the general principles of GCP 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 origin, follow up to subjects after end of the clinical trial).

Clinical trials with ATMPs which are performed in the EU should comply with the requirements in Regulation (EU) No 536/2014 on clinical trials.[3]

[1] 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).

[2] The International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ('ICH') reached a consensus in 1995 to provide a harmonised approach for good clinical practice.

[3] Regulation (EU) No 536/2014 on clinical trials 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, 2004 OJ L158/1.
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, 2001 OJ L 121/34.)

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, offspring, close contacts, investigator's team and others. In particular, the following should be taken into consideration:

(i) 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:

- For populations that might ultimately be amenable to organ transplantation or transplantation of haematopoetic stem cells, sponsors should consider whether exposure to the ATMP would cause sensitization and potentially compromise future transplant success.

- When the clinical trial subjects involve a paediatric population or foetuses (in utero treatment), 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. Thus, in some cases, it may be advisable to stagger trials by age *i.e.* first enrolling subjects between 18 and 12 years, then between 12 and 6 *etc*. However, in some other cases (*e.g.* severe genetic diseases), treatment of the subject at a very young age may be necessary without a staggered approach.

  Prior studies in adults should have been performed if feasible for the condition in question, or else a rationale should explain why these are unethical, not feasible or not relevant (e.g. in cases of diseases exclusively affecting paediatric patients).

- The relation of the anticipated benefits to the risks of the ATMP should be at least as favourable as existing alternative approaches. Particular consideration should be paid in cases where the treatment is irreversible or if the administration of the ATMP prevents the subject from accessing to future therapies (*e.g.* immunogenicity in case of gene therapy).

(ii) For some ATMPs an intra-subject control might be appropriate. For example, the investigational product could be injected into one eye and the untreated eye is used as a control. Comparison of local effects can be facilitated in this way by eliminating inter-subject variation.

(iii) While comparison to standard of care or no treatment sometimes makes double-blinding not feasible for investigators/for the surgical investigator team, blinding for subjects should take place where feasible.

(iv) 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 an unreasonable risk. The risk posed by the procedure should be duly explained in the protocol.

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

In early phase trials where it is not possible to re-administer the product (*e.g.* gene therapy) or when the re-administration involves the additional risk of a surgical procedure, the exploratory dose chosen should aim to be a therapeutic dose for the subject.

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

(vii) The cohort size number usually depends on disease prevalence and manufacturing capacity. The sponsor should select a cohort size feasible and adequate to meet study objectives.

3. Application dossier

The content of the application dossier, including the protocol and investigational medicinal product dossier is described in Annex I to Regulation (EU) No 536/2014.

Where an ATMP contains cells or tissues of human origin, the application 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[4] or Directive 2002/98/EC,[5] and

- the confirmation that there is a traceability system 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[6].

3.1. Specific considerations concerning the protocol

The following should be considered by the sponsor of a clinical trial involving ATMPs in relation to the content of the protocol:

(i) *Release specifications*: The variability in the nature of the ATMPs (in particular in the case of autologous products or allogeneic products in a matched donor scenario), should

[4] Directive 2004/23 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, 7.04.2004,p.48).

[5] Directive 2002/98 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).

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

be duly considered when defining the release specifications (*e.g.* cell numbers/range of cell numbers, transduction efficiency).

(ii) *Dosing*: Early phase clinical trials should attempt to define the dose range to be used in the pivotal trial. However, unique difficulties may arise in determining the dose for some ATMPs in early phase clinical trials, for example:

- 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 which assist in the mechanism of action of the ATMP, for example in transduction efficiency.
- For some autologous products or subject specific allogeneic donor products, the cell numbers may vary for each dose due to the intrinsic variability of the starting materials.

Therefore, it is acknowledged that in the case of some ATMPs it may not be possible to perform formal dose finding studies.

(iii) *Upstream interventions on subjects*: In an autologous setting, the subject must undergo a medical intervention to extract cells/tissues prior to the manufacture and administration of the 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, it is important that such processes are clearly explained The level of documentation should be adapted to the complexity and the novelty of the procedure.

(iv) *Administration procedure*: Information on the administration of the investigational product should be provided when the administration requires specific concomitant therapy and/or involves surgical procedures that could have an impact on the safety or efficacy of the product. This includes information on the standardisation and optimisation of the processes involved, including -where applicable- the surgical procedures.

The description of the administration process should be sufficiently detailed. The level of documentation should be adapted to the complexity and the novelty of the procedure.

(v) *Safe conduct*: Detailed information should be provided on the product handling, containment and disposal.

(vi) *Risk-minimisation measures*: Where appropriate, information should be provided on the measures that should be put in place to protect clinical trial subjects from identified risks. For example, if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including liaison with clinical staff where out of specification test results are obtained after the release of the product.

(vii) *Definition of end of the trial*: The definition of "end of the trial" should be clear and unambiguous. Due to the novelty and scientific uncertainties that exist in connection with ATMPs, there may be a need for subjects 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 how follow-up activities will be performed after the end of the trial (*e.g.* via an interventional study, non-interventional study, registry).

(viii) *Follow-up strategy of subjects*: If the ATMP has the potential for prolonged biological activity after a single administration, long-term follow-up of subjects should be envisaged, The follow up strategy should be based on a risk-assessment having regard to all information available to the sponsor. This strategy may need to go beyond the end of the trial. For example, in the case of gene therapy medicinal products using integrating vectors, a follow-up of 15 years after administration is expected.

Follow up to subjects treated should be ensured also in cases of early termination of the clinical trials.

(ix) *Combined ATMPs*: Where an ATMP incorporates a medical device, the protocol 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 the EU legislation on medical devices for the intended use. When this is not the case, a justification should be provided and compliance of the medical device component of the combination product with the relevant general safety and performance requirements set out in Annex 1 of the Medical Regulation 2017/745[7] must be documented in the protocol.

(x) *Gene therapy*: In case of ATMPs involving viral vector based gene therapy, information on viral shedding and any precautions required should be provided, where applicable.

3.2 Specific considerations regarding the Investigator's Brochure (IB)

The following should be considered by the sponsor of a clinical trial involving ATMPs in relation to the content of the Investigator's Brochure:

(i) Non-clinical studies: The rationale for the non-clinical development should be discussed and justified. Non-clinical studies should be carried out with the most appropriate and relevant in vivo- and in vitro models.

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 some cases, testing the medicinal product in animals may not give sufficient meaningful information about the safety profile of the product in humans. In contrast, testing animal cells in animal models does not permit either to predict the safety profile of the actual medicinal product. It follows that the ability of

[7] Regulation (EU) 2017/745 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 applies.

preclinical 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 preclinical 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*.

(ii) *Information on the product*: The investigator's brochure should provide comprehensive information on the risks of the product (based on existing knowledge), including risks associated with administration procedure, long-term safety issues specific to ATMPs such as tumorigenicity, immunogenicity/immunosuppression, risks related to infection with vectors used in gene therapy medicinal products, *etc*.

Information should also be provided on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the targeted disease on the product, or vice versa (*e.g.* an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction). The risks of treatment failure should also be addressed where appropriate.

(iii) *Reconstitution*: When the 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.* when the reconstitution involves thawing, the rate of temperature change during thawing should be described.)

The reconstitution should be described in the protocol. It is acceptable that the detailed instructions are laid down in a separate document available at the site (*e.g.* handing instructions), in which case a reference to such separate documents should be provided in the protocol.

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

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

(iv) *Administration procedure*: When the administration process is not standardised the detailed instructions for administration should be described in the protocol or in a separate document available at the site (e.g. handing instructions), in which case a reference to such separate documents should be provided in the protocol. Where appropriate (i.e. in the case of complex administration procedure), training should be provided to those involved in the process.

(v) *Dosing*: In case of ATMPs with complex dosing regimens, there should be adequate explanations for the rational to ensure an adequate level of understanding and compliance by the investigator and those involved in the clinical trial.

(vi) *Safety of the clinical trial subject:* information on short and long term safety issues particular to ATMPs such as infections, immunogenicity/immunosuppression and malignant transformation should be provided. Where appropriate, there should be clear information on risk-minimisation measures (*e.g.* detailed instructions on how to proceed if the product is administered before the results of the sterility test are available and the product is contaminated, instructions on how to contact the clinical trial subject if a health concern is identified in the donor of the starting material, *etc*.)

(vii) *Safe conduct of the clinical trial*: detailed information should be provided on the product handling, containment and disposal. The level of information should be adequate having regard 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 of gene therapy products where there is a risk of viral shedding, adequate information on the measures to implement to address this risk should also be provided.

(viii) *Traceability*: detailed information should be provided on the measures that should be followed to ensure traceability of the cells/tissues contained in ATMPs.

4. Quality of the investigational ATMPs

Investigational ATMPs should comply with the Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products.[8]

The quality of ATMPs may be highly dependent on the storage, transport and handling conditions. The sponsor should provide the investigator with detailed instructions for the handling and storage of investigational product(s) for the trial. The risks to those handling the product and close contacts as well as, where applicable, the risks to the environment should be clearly explained.

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 subject administration to enable verification of the quality of the product.

In case of complex handling processes or when reconstitution is required, the sponsor should provide the investigator with adequate training.

[8] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

5. Administration procedures

The administration procedure should be clearly explained by the sponsor. The level of documentation should take into account the complexity and the novelty of the procedure.

When the administration requires specific concomitant therapy and/or involves surgical procedures that could have an impact on the safety or efficacy of the product, the sponsor should train the investigator on the use, application, implantation, administration and/or co-medication procedures. The investigator should, in turn, ensure that all staff involved in the administration process are trained on the particular requirements for the application of the ATMP.

The presence of the sponsor (or a representative thereof) during the administration of the ATMP to the clinical trial subject is only acceptable if it is duly justified. If the presence of the administration 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 of administration, the clinical trial subject should be informed *a posteriori*.

6. Traceability

The use of each investigational medicinal product should be traceable. The individual product should be traceable from delivery to the investigator up to the administration to the clinical trial subject. Non-administered investigational products should be returned and/or destroyed and should be accounted for.

Moreover, 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.

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 regarding traceability. 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. In the case when the sponsor ceases to exist, the custody of the traceability data should be discussed with the competent authorities.

The requirements for traceability are without prejudice to the provision 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. Therefore the system should allow full traceability from the donor to the recipient through an appropriate coding system.

7. Retention of samples

Under general GCP principles, the sponsor should maintain sufficient quantities of the investigational medicinal 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 scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep samples of 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.

8. Protection of clinical trial subjects

8.1 Informed consent

Subjects that participate in a clinical trial with ATMPs should receive adequate information on the risk of the product, including risk of treatment failure and effects of the treatment on future therapies typical for the diagnosis or treatment of the disease.

Where applicable, the subject should also be informed of the irreversible nature of the ATMP.

The need for long-term follow-up should be clearly communicated, where applicable, and subject commitment should be sought.

In case the ATMP includes a bacterial or viral vector and thus a potential for "shedding", the risks and precautionary measures should be clearly communicated to the subject.

The subject should be informed when the sponsor (or a representative thereof) is present during the administration procedure as explained in Section 5.

8.2. Long-term follow-up

8.2.1. General principles

The need for and the duration and the nature of follow up (*e.g.* interventional study, non-interventional study, registry) should be described in the clinical trial protocol. It is

recommended that the sponsor considers discussing the duration of follow up with the concerned national competent authority.[9]

Where applicable, it should be clearly specified which follow up activities should take place prior to and after the end of the clinical trial.

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 (*e.g.* registry, post-marketing studies).

8.2.2. Remote follow-up

Clinical trial subjects may enrol to participate in a clinical trial that is conducted far away from their place of residence. In particular in cases where clinical trial subjects should be followed for a long period time, clinical trial subjects may not be willing to return to the investigator site for the follow up.

Detail arrangements for the remote conduct of follow-up activities should be explained in the protocol or an associated document. In accordance with applicable requirements, the sponsor should ensure that approval of a clinical trial protocol is obtained in the country where the long term follow-up takes place. In EU/EEA such follow-up of a clinical trial in a different Member State /EEA country compared to where the treatment was given requires an application for an additional Member State concerned to be added.

8.2.3. Premature end or termination

If a subject stops participation in the trial or does not want to continue administration of the product (repeated dosing), 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.

The sponsor should ensure that there is a process in place for follow up of the subjects treated with the product even 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.

8.2.4. 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 to inform treating physicians about the product used with a view to facilitate medical care of the patients in case of an emergency and to facilitate reporting of adverse events.

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

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

8.3. Administration of out of specification products

As explained in Section 3.1, the variability in the nature of the ATMPs should be taken into account when defining the release specifications.

Exceptionally, in case where the release specifications as set out in the protocol 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 sponsor should provide him/her with its evaluation of the risks and notify him/her that the out of specification product is being supplied at his/her request. The confirmation of the investigator to accept the product should be recorded by the sponsor and the relevant competent authority should be notified of such events (as an urgent safety measure or breach of predefined specifications).

9. Safety Reporting

Where appropriate, report forms and data capture systems (SAE forms; CRFs for recording of adverse events) should be adapted to reflect a differentiated causality assessment for each of components of the ATMP (e.g. the cell-based part and 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 application process (surgical procedures; or other),
- adverse events possibly related to medical devices which 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 related possibly to mandatory concomitant medication (e.g. immunosuppression).

The sponsor should provide information and 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.

10. Monitoring

The sponsor should adequately monitor the conduct of the clinical trial as provided for under Article 48 of the Regulation (EC) 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. If the IMP records required to maintain traceability are used for this purpose at the investigator 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).

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