Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the EU

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INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific issues in the context of clinical trials (CT). Several normative instruments apply at the European level (see table opposite). The 2019 guidelines from the European Commission on Good Clinical Practice (GCP) both adapt the ICH E6 to ATMPs' characteristics and provide necessary additional measures. However, they are not exhaustive as they explain only some specificities of ATMPs and they remain complementary to the general rules. We will highlight the specific requirements for investigational ATMPs (ATIMPs) to reveal the particular challenges they are addressing and why these challenges warrant separate regulation in order to obtain CT' authorisation for ATIMPs and potentially for further marketing authorisation application (MAA).

Text Level	General	ATMPs
Legal	Regulation 536/2014 on clinical trials	Regulation 1394/2007 on ATMPs
Regulatory guidelines	ICH E6 on GCP	Specific GCP

ATMPs Guidelines content and potential challenges targeted

Clinical trials design

1. **Study population**
   ATMPs characteristics > Subjects' risks & benefits, interpretable data
2. **Cohorts**
   Limited manufacturing capacity > Staggered treatment
3. **Comparators**
   No active comparator > Best standard of care, or intra-subject control
4. **Blinding**
   Double blinding unethical/ unfeasible > For subjects' where possible; blinded observers if unblinded investigator
5. **Placebo**
   Invasive procedures > No more than minimal risk/burden for control groups
6. **Dosing**
   Identifying active cells; inactive particles with impact; dose variation of cells numbers; complex dosing > For long-term effects, dose escalation & repeated dosing Or exploratory dose = therapeutic dose
7. **Trial end**
   Potential need for long-term follow-up > Clearly defined event marking trial end

Quality

1. **General considerations**
   ATMPs characteristics > Compliance with GMP for ATMPs
2. **Starting materials**
   Variability > Compliance with directives on blood and cells/tissues; Traceability system's with bidirectional tracking
3. **Storage, transport & handling conditions**
   e.g., temperature, short-shelf life > Timelines in trial records; Investigator's training
4. **Reconstitution before administration**
   Potentially complex > use of solvents and/or other materials?; Training
5. **Medical devices (MD)**
   Combined ATIMP > MD characteristics, performance and intended use + MD Regulation Compliance OR justification of MD suitability for intended use
   MD used with ATIMP > List of investigated MD; statement on CE-marked MD; MD characteristics, performance, intended use, and regulatory status

Upstream intervention on subjects and administration procedures

1. **General**
   In autologous setting, deviation from standard clinical practice > Subject's risks + impact on product quality and safety;
   Procedure complexity and novelty > Adapted level of documentation; Training
   Possible necessary sponsor presence during administration or in any upstream collection procedure > justification
2. **Traceability**
   If human origin Cells/ tissues > Bidirectional traceability system (anonymous coding); 30 years data keeping; Role and responsibilities of manufacturer, sponsor and investigator & location of traceability records to be documented
3. **Retention of samples**
   Materials' scarcity > Autologous ATMPs and certain allogeneic ATMPs: justified not to keep samples; Possible sampling strategy adaptation;
   Short shelf-life > Shorter retention period; Manufacturer to consider conditions for prolonging shelf-life;
   Samples cannot be kept > Retained label Photographs or copies

Monitoring

Human origin of cells/tissues >
Traceability requirements/ long-term follow-up arrangements compliance;
For ATIMPs accountability records kept at CT site, possible requirement of adaptation of study requirements' form, records reflecting ATMPs specificities

Administration of out of specifications products

Variability in ATMPs nature >
Exceptionally to avoid immediate significant hazard; manufacturer/ sponsor to provide risks evaluation; records of request kept in manufacturing site; relevant authority to be notified

Non-clinical studies

Safety: Incompatibility between human & animal species > Case by case assessment of non-clinical data

Information in Investigator Brochure and Protocol

Placebo: Procedure's risk
Dosing: For complex dosing ATMPs, adequate level of understanding & compliance by investigator and those involved in CT
End of trial: how follow-up activities will be performed after end of trial

Product information in IB:
- product risks;
- previous/ concomitant (or required further treatments) potential impact;
- treatment failure risk;
- emerging issues

Risk minimization measures: Where appropriate, measures to protect CT subjects from identified risks:

Quality: reconstitution before administration: Description of Reconstitution

Upstream interventions on subjects and administration procedures: Detailed instructions, possibly in separate document available at site if attached as Annex

Long-term follow-up general principles & remote follow-up:
- Follow-up scheme & after trial follow-up activities;
- Detailed arrangements for remote conduct of follow-up;
- How to ensure collected data quality

CT Safe conduct

1. **ATIMP Handling**
   Infectious biological material > Handling and disposal detailed instructions
   Bacterial/viral vector with shedding potential > Risks and precautionary measures for subject and/or caregivers
   Risks for health care professionals > Risk minimisation measures
2. **Risk minimization measures**
   e.g. No sterility test result at product release; CT subject risk of cytokine release syndrome > Mitigation measures; Information to Investigator on measures before treatment

Long-term follow up

1. **General principles**
   Safety profile not fully elucidated > Duration of ATIMP biological activity; long term follow-up scheme; Length of observation period; relevance of other product bibliographic data; not required if low risk of delayed adverse events; monitoring of CT subject follow-up in MAA
2. **Remote follow-up**
   e.g. distance from residence > Gathering data process; Sponsor responsible for adverse events collection robust system; Writing of each party involved responsibilities; Collected data centralisation & availability for inspection at CT site
3. **Premature end or termination**
   Specificities where CT subjects will and foreseen long-term follow-up
4. **Patient card alerts**
   For CT subjects depending on ATMPs characteristics to inform treating physicians to facilitate medical care in case of emergency & reporting of adverse events

Protection of CT subjects

Uncertainties, novelty… >
Informed consent: CT participant information on all risks, e.g., treatment failure, irreversible ATIMP nature…

Safety reporting

ATMPs characteristics > safety concerns > Adapted reporting forms & data capture systems; List of safety issues; Sponsor to provide information/ training to investigator for adverse events reporting; Foreseen long-term follow-up to include reporting of adverse events

CONCLUSION

Very useful ATMPs specific guidelines for clinical trials covering many different aspects and all currently identified challenges

Necessary case by case evaluation of the various aspects of ATIMPs clinical trials mainly due to variability of starting materials and specific characteristics of each ATMP. Various levels of justification and documentation to be provided for clinical trials authorization

→ Particularly relevant to engage in a pre-CT application meeting with regulatory agencies, such as the French National Agency (ANSM) as it is proposed in France

REFERENCES

European Commission, Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Products, 10 October 2019, C(2019) 7140 final.

European Commission, Guidelines of 22 November 2017 on Good Manufacturing Practice for Advanced Therapy Medicinal Products, C(2017) 7694.

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; OJ L 33, 8.2.2003, p. 30–40.

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 L 102, 7.4.2004, p. 48–58.