What specificity for the clinical aspects of investigational advanced therapy medicinal products?

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BACKGROUND AND AIM

While Advanced Therapy Medicinal Products (ATMPs), an European legal classification of medicinal products based on genes, cells and tissues, raises specific quality issues, the latter are particularly acute in the context of clinical trials and thus cannot be treated as any other medicine, notably because of their manufacturing constraints and short shelf-life. In comparison to more traditional medicinal products, ATMPs have been subject to specific regulatory provisions in the European Union (EU) since 2007. In addition, many guidelines have also been adopted to consider the issues raised by ATMPs.

Clinical trials with ATMPs are generally governed by Regulation 536/2014 on clinical trials, which came into effect on 31 January 2022, as well as ICH E6 Guidelines on Good Clinical Practice (GCP). For clinical trials conducted in the EU, it is mandatory to comply with GCP. Most importantly for investigational ATMPs, the European Commission has adopted and published 2019 Guidelines on GCP specific to ATMPs, as required by Article 4 of Regulation (EC) n°1394/2007 on ATMPs. These guidelines are both adapting ICH guidelines to ATMPs characteristics and providing additional measures that have been considered necessary. However, they are are not exhaustive as they explain only some specificities of ATMPs and they are complementary to the general rules. Not only are these guidelines targeting ATMPs specifically, they also have a dedicated section on the quality of investigational ATMPs.

The aim of this poster is to highlight the specificity of quality requirements of investigational ATMPs in order to reveal the specific challenges they are addressing and why these challenges deserve separate regulation in order to demonstrate quality in clinical trials.

METHODOLOGY

The research work has consisted in examining the elements of the 2019 Guidelines from the European Commission that were dedicated to the quality of investigational ATMPs, in order to analyze them through the lens of the corresponding scientific literature.

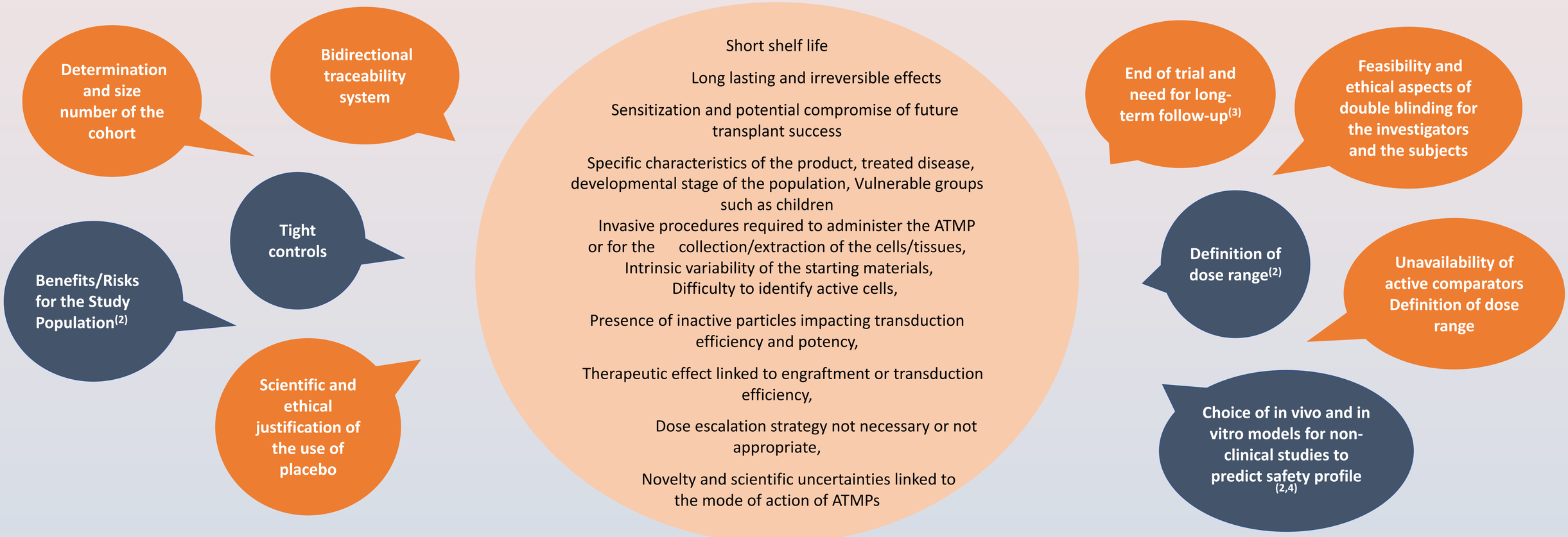
The first stage of the research has consisted in the study of aforementioned guideline through the analysis of the general structure of the guidelines regarding the challenges covered, and a more detailed analysis of the quality aspects, especially regarding the section on the quality of investigational ATMPs. More specifically, the subsections of the guideline that were relevant to the analysis of specific quality requirements for investigational ATMPs were identified. Then, the main issues at stake for each subsection were formulated and organised by topic.

During the second stage of the research, a literature review was conducted in PubMed and Web of Science, using queries such as ("Investigational Advanced Therapy Medicinal Products") or ("Advanced Therapy Medicinal Products" AND "Clinical Trials" [Title]). The research generated 29 results, among which only 4 articles were selected for further content analysis, on the basis of their relevance for the study of specific quality requirements for investigational ATMPs at the EU level of governance.

At the last stage of research, analysis of the literature was compared to the results from the guideline analysis.

RESULTS

Main challenges for ATMPs: the design and conduct of clinical trials



Conclusion

Case by case evaluation of the various aspects of the design of the early-phase ATMPs clinical trials and various levels of documentation to be provided for clinical trials authorisation

Guidelines' specific requirements concerning the quality of experimental ATMPs

General considerations

Compliance with the European Commission Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

Starting materials

- Impact of the variability of donor or patient based starting material to define release specifications for cell-based ATMPs (for autologous product: disease status of the patient)
- Confirmation of compliance with European directives on quality and safety of human tissues and cells, and human blood and blood components for their donation, procurement and testing
- Confirmation of the traceability system's establishment with bidirectional tracking of tissues and cells from donation to administration

Storage, transport and handling conditions

- Detailed instructions of the reconstitution process from sponsor to the administration site:
  - To specify if the reconstitution requires the use of solvents and/or other materials
  - Reconstitution to be described in the Investigators Brochure or in its Annex
  - For complex reconstitution process: training to be provided

Investigational ATMP Reconstitution before administration

- Detailed conditions from sponsor to investigator (e.g., temperature conditions)
  - When short-shelf life: timelines to be clearly documented in trial records
  - For handling processes: adequate training of the investigator

Medical devices (MD)

- MD integrated within the investigational ATMP (combined ATMP):
  - Information on the characteristics, performance and intended use of MD, **AND**
  - Compliance with the relevant MD general safety and performance requirements (Regulation 2017/745), **OR** justification of the MD suitability for the intended use on the basis of these requirements
- MD used with investigational ATMP (not integrated):
  - Cover letter with:
    - List of MD to be investigated in the clinical trial
    - Statement on the existence of CE-marked for the MD intended use.
    - Summary information on characteristics, performance, intended use, and regulatory status of MD

DISCUSSION AND CONCLUSION

Many different aspects are covered in this guideline. They are **essential to patients' well-being and product safety**. They permit to **avoid mistakes and minimize risks through the design and the conduct of clinical trials**. As such, they guide medicines' developers in the innovative sector of ATMPs.

ATMPs are innovative and more complicated than traditional or other biological drugs → precise and specific requirements which can raise logistical issues, such as the adaptation needed in terms of equipment and logistics(2).

High risks associated with the manufacturing process and the product → higher expectations for control

Many sources of variability can influence the quality of the investigational ATMPs → they should all be considered and minimized to avoid distorted results(5)

Variability can lead to the discontinuation of the clinical trial although it can also be related to a strategic decision of the sponsor, the poor recruitment of clinical trials' participants or serious adverse events(5)

For phase 1 clinical trials, quality and safety strongly overlap.

Solution to address the challenges of quality in the context of ATMPs clinical trials: to engage in a pre-clinical trials application meeting with regulatory agencies, such ANSM as it is proposed in France(4)

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