Health by Advanced Therapies

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Roadmap of WP3
Roadmap of the needs and strategy of clinical Research for Advanced Therapies
Public

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1. Deliverable's description

This document describes the roadmap of Work Package 3 of RESTORE: Definition of the Needs and Strategy of Clinical Research for Advanced Therapies. The purpose of this document is to outline the major challenges in clinical research for Advanced Therapies, and to outline the strategies RESTORE intends to employ to overcome these hurdles.

Objectives

To build a roadmap outlining how RESTORE aims to tackle the challenges in clinical research in the field of ATMPs, including safety and legislations surrounding clinical trials and how to de-risk the clinical development of Advanced Therapies. As such, we have divided the road map into 2 main topic areas:

I. Regulatory science and early health technology assessment
II. Early clinical trials and refined translation

Within these areas, RESTORE proposes strategies that aim to push forward advances in Advanced Therapies themselves, as well as strategies that will increase the pace of translation and development of ATMPs as commercial products by standardisation of protocols across the EU. The road map is a constantly evolving document that we are working on and improving continuously as RESTORE develops.

Road map; Definition of the Needs and Strategy of Clinical Research for Advanced Therapies.

2. Regulatory science and early health technology assessment

2.1. State of the art

Gene editing: In the field of gene therapy medicinal products, an alternative approach to the classical use of viral vectors is genome editing. The most prominent platform currently is CRISPR/Cas9-based gene editing that enables researchers to precisely and permanently modify the genome of all kinds of human cells for therapeutic purposes.

Combined ATMPs: Where an ATMP is incorporated as an integral part of the medicinal product or medical devices, the combination may qualify as a combined ATMP. An example would be tissue-engineered products that entails the seeding and culturing of differentiated somatic cells onto biodegradable scaffolds, which is then implanted into the defective or damaged sites to regenerate tissues.

Genetically modified organisms (GMOs): Gene Therapy Products are genetically modified organisms (GMOs). "Genetically modified organism (GMO)" means an organism, in which the genetic material has been altered "unnaturally" in a way that does not occur naturally by mating and/or natural recombination.

- Additional requirements for an investigational medicinal product (IMP) that has a GMO component: In addition to submissions to national competent authorities and ethic committees, IMPs containing GMOs must get GMO approval from environmental/regulatory authorities before a clinical trial can commence.
- There are two main directives that gene therapy developers must comply to:
  - Deliberate release directive (Directive 2001/18/EC) - GMO considered to be in wide use with fewer, or no, containment measures
  - Contained use directive (Directive 2009/41/EC) - GMO considered to be used in a controlled or contained setting.

2. 2 Major challenges and roadblocks to be addressed

a) Gene edited products:

- Specific challenges to developers may include the thorough analysis of off-target activity by tools that combine *in silico* and *in vitro* methods.
- For *in vivo* gene editing approaches, it may be required - but also challenging - to conduct a non-clinical bio-distribution study to gain information on the dissemination of the applied product.
- It can be difficult to fully characterise the final product with analytical assays, especially when the product's mechanism of action may not be fully understood.
- Another major challenge is the inherited variability existing in these products, which makes them ineligible for scalability in late-phase clinical trials.

- Bioreactors as an emerging strategy for automated production are also being intensively researched as means for scaling up/out manufacturing and reduce sources of contamination. Developers are still struggling to figure out the optimal regulatory pathway for these emerging manufacturing technologies.
- Developers should be encouraged to have frequent interactions with regulators to ensure useful feedback on above challenges.

b) Combined ATMPs

There is a need for more clarification on the classification of combined ATMPs especially in borderline cases as the classification requirements can raise uncertainty. A combined ATMP is classified as such when the device element of the ATMP is an integral part of the final product and alone might be classified as medical device whereas the combined component is considered as an "excipient" if it is not or no longer used as a medical device.

c) Genetically modified organisms (GMOs):

- GMO legislation is not designed for medicines but originally intended for the agri-food sector
- GMO legislation is interpreted and implemented differently across Member States, e.g. different definition of GMOs (due to differential use of Deliberate Release and Contained use Directives)
- Data requirements for environmental risk assessment (ERA) vary in each Member State depending on which directive they are using:
    - Deliberate release: Data requirements focused on scientific/ technical information
    - Contained use: Data requirements focused on the details of facilities precautions for handling, etc.
- Different authorities for CTAs and ERA
    - CTA – Competent authority for clinical trials
    - ERA – Environmental agency
- Lack of harmonisation between GMO and CTA requirements
- Variable timelines and processes across Member States
- In contrast to the US where clinical trials with GMOs IMPs do not require a GMO approval procedure, GMO approvals in Europe may delay GMO Clinical Trials
- New CT Regulation (No 536/2014) does not address GMOs
- Different definition of GMOs across Member States (due to differential use of Deliberate Release and Contained use Directives)

2. 3 Overall Goals

To develop strategies on tackling the regulatory challenges of ATMPs, particularly combined products and gene edited products as well as GMO-containing IMPs.

2. 4 Scope- Where can RESTORE make a difference

Short-term (next 3-5 years)

For Gene Edited Products: Explore the regulatory suitability for novel and reliable biological control tests that can demonstrate efficacy, specificity, and safety (incl. off target effects) in the targeted tissue.

For combined ATMPs: Ask for further guidance on handling of borderline and combined ATMPs to enable a transparent and predictable classification process.

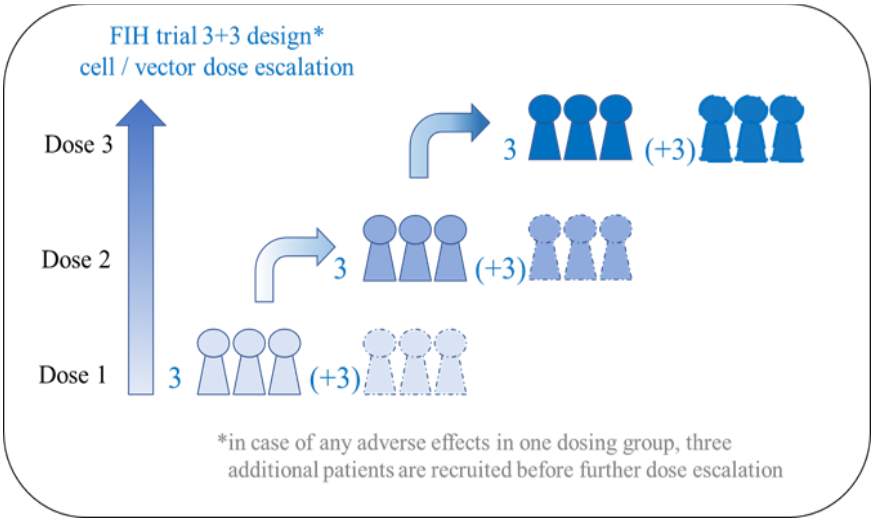
For GMO:

Present strategies for harmonisation in timelines and data requirements where possible (with national agencies being lobbied to ensure the new Clinical Trial Regulation (CTR) is not compromised)
Ask for further guidance at member state level to make the pathway clearer for developers
Ask European Commission to produce a list of requirements and work with agencies and member states to encourage convergence. An important issue to raise would be the definition of a GMO. To this end, specific attention will notably be paid to the national implementation (and its potential variation) of the recent decision of the Court of Justice of the European Union stating that organisms obtained by mutagenesis are GMOs as long as the genetic material is altered in a way that does not occur naturally.

3. Early clinical trials and refined translation

3.1 State of the art

- Early Clinical Development (CD) of conventional drugs starts mostly with First-in-Human (FIH) in healthy probands and moves then to the targeted patient group(s) applying a structured dose escalation scheme.
- Early CD of Advanced Therapies combines mostly Phase I/IIa (Safety/PoC) and starts in the targeted patient population (commonly not in healthy probands); there are used limited dosing groups (mostly 3+3 design)



- Currently, >300 and >500 phase I and phase II trials, respectively, are running on Advanced Therapies worldwide (Alliance Regenerative Medicine Report 2018)

3.2 Major challenges and roadblocks to be addressed

- There is a high failure rate of novel (conventional) drugs in late clinical development (phase I 16% phase II 62% phase III 33 %) indicating there is a high need for better understanding of
  - drug candidate selection
  - dosing
  - surrogates for therapy response
  - better models for mapping molecular targets distribution and possible off-target effects
  - markers for patient stratification during late preclinical and early clinical development (phase I/IIa) to prevent unsuccessful expansive late clinical trials (de-risking strategy)
  - non-invasive techniques to monitor success at early stages, and in a quantitative manner, are sorely needed
- In principle, this is true for Advanced Therapies (regulatory: ATMP) as well (less data available) but there are several special issues:
  - Limited value of preclinical models currently used (=> WG Preclinical model systems)
  - Special regulatory issues => WG Early clinical trials and refined translation
  - Typically, different design of early clinical trials compared to conventional drug candidates; need for efficacy parameters already in early trials

- EU: clinical trials are authorized at national level, which naturally leads to discrepancies (improvement planned)
- (Micro)heterogeneity of the ATMPs (esp. [autologous] cell-based products), further increased in early CD due to less robust manufacturing and supply chains (=> WGs manufacturing: somatic and gene-modified cells, manufacturing: *in vivo* gene therapy, manufacturing: tissue engineered &composite products), can impact case-by-case outcome (esp. autologous products)
- up-scaling for late stage trials can strongly modify the product quality, and can impact patient response compared to early clinical trials
- Many FIH/early clinical trials take place in an academic environment, including manufacturing and delivery
- Paediatric patients have particular requirements, and therapeutic approaches must be adapted. In the case of cell therapies, undifferentiated phenotype of paediatric cells could provide additional benefits and constitute an improved therapeutic arsenal for both autologous and allogeneic use.

Pros: high innovation level, strong link to basic science feasible, driven by medical need
Cons: limited resources and experiences, incomplete risk-based approach (RBA)

- FIH/phase I/IIa studies address not only safety endpoints; efficacy endpoints are requested more and more by regulatory authorities
  - need for defining efficacy parameters
  - appropriate controls needed to establish efficacy (blinding, placebo, etc.) – placebo control is more complicated in ATMP trials but feasible
- early definition which regulatory pathway will be envisaged up to marketing entry to prevent adaptation/restart later (e.g. PRIME, rare diseases etc. – complex process)
- Complexity of mode-of-action (often not fully known) shatters current paradigms of PK/PD
- no clear dose-response relationship regarding safety and efficacy
- strong impact of (autologous) source of raw material
- bio-distribution, half-life, and fate of "living drugs" are hardly to determine

3.3 Overall Goals

To implement an early Clinical Trial platform that supports innovative early clinical trial strategies to accelerate and de-risk the Clinical Development (CD) of Advanced Therapies.
To explore what institutional and regulatory supports have been developed in EU MS, especially for ATMP
<u>Key elements:</u>

- Refined Translation (iterative improvement during early CD)
  - More data about the ATMP (preclinical models & product characteristics) (=> WGs manufacturing: somatic and gene-modified cells, manufacturing: *in vivo* gene therapy, preclinical model systems)
  - more data about molecular targets (advanced methods to map distribution, affinity, ontogeny, physiological analogs in expression in different populations and at different developmental stage)
  - More data about the patient response to therapy (biomarkers)
  - Tools to non-invasively track and quantify bio-distribution of cell therapies in humans
  - Handling Big Data (=> WG Big data/ AI)
- Adaptive clinical trial design (e.g. "basket" phase I/IIa trials)
- Regulatory Science and early HTA (=> WG early clinical trials and refined translation)
- Capturing patient experience in early clinical trials already (e.g. Patient-Reported Outcome measures …)

- Pharmacovigilance program for advanced therapies in consonance with the European Medicine Agency and other regulatory agencies.
- Structural elements:
- Qualified Academic Translation Centres of Excellence (Hub´s): network of academic translation centres with tissue acquisition, cell manufacturing and phase 1b/2a trial implementation capacity. Strong interaction with regulatory authorities and focus on efficient VHP approval.
- One-Stop-Service for consultancy

3.4 Scope- Where can RESTORE make a difference

Long-term Vision (8-10 years):

- Pan-European ecosystem provides synergies for CD of novel Advanced Therapies
- Implementation of AI into early CD (product optimization, patient selection …)
- Higher success rate of late clinical trials if passed RESTORE early CD (failure rate tbd)
- Visible and measurable progress of next-generation Advanced Therapies
- Pan-European Pharmacovigilance of ATMP

Short-term (next 3-5 years)

- Role models proved for application of AI into early CD (product optimization, patient selection)
- Toolbox "biomarkers" available for mechanistic side studies
- Several new next-generation AT products in clinical testing (e.g. iPSC-derived products, next-generation Treg, CAR/TCRtg-T to solid tumours, next-generation *in vivo* gene therapy …)
- Patient registry on AT trails is running
- To establish a new paradigm in the treatment of a wide range of human diseases by exploding the effector capacity of immune cells (i.e CAR T cells, NK cells) or homeostatic and suppressive skills of regulatory cells (Treg, MSC).
- Developing Personalised Medicine (PM) for an optimised strategy for prevention, diagnosis and treatment of disease for each individual person, based on his or her unique characteristics.

Define "universal" cell products applicable as "master" cell products with minor modification for different indications, e.g. MSC, Treg, CAR-T …

3.5 Expected key deliverables for 4-5 years

- Definition of criteria for Translational Centres of Excellence
    - Pre-requirement criteria for application (regional/national co-support)
    - Key performance indicators
    - Open call year 1, evaluation year 4
- One-stop-service offering advice for preparing early clinical trials (blueprints in collaboration with translational centres of excellence and industry partners, guidance on regulation) in collaboration with regulatory authorities
- One-stop-service offering off-the-shelf validated biomarker panels and advice for the development of new biomarkers for monitoring therapy response and patient stratification (in collaboration with translational centres of excellence and industry partners)
- Based on permanent collection of experiences from RESTORE community, identification of bottlenecks in CD of Advanced Therapies and figuring out solutions (collaboration with regulatory authorities)
- Building-up registry of all patients in clinical trials of RESTORE network
  White paper on Early Clinical Development of Advanced Therapies.