Health by Advanced Therapies

D3.4
Strategy paper on innovative early and late clinical trial design and regulatory rules for Advanced Therapies
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List of Acronyms

ATMP(s): Advanced Therapy Medicinal Product(s)
CMC: Chemistry Manufacturing and Controls
CT: Clinical Trial
CTA: Clinical Trial Authorization
ERA: Environmental Risk Assessment
FTO: Freedom To Operate
GMO(s): Genetically Modified Organisms
GMP: Good Manufacturing Practice
HTA: Health Technology Assessment
IP: Intellectual Property
NHS: National Health System (please note that this acronym refers to any National Health System and not specifically to the UK National Health Service)
RWE: Real World Evidence
WG(s): Working Group(s) here refers to the scientific working groups created by the Restore Projects to analyse the challenges at the different steps of development of ATMPs. Here below the full list of RESTORE WGs:

- WG 1: Manufacturing: (modified) cells
- WG 2: Manufacturing: Tissue Engineering & Composite Products
- WG 3: Manufacturing: In vivo gene therapy
- WG 4: Manufacturing: pluripotent stem cells
- WG 5: Manufacturing: Ex vivo gene delivery/editing
- WG 6: Pre-clinical model systems: In vitro and in vivo
- WG 7: New Clinical Applications: Endogenous regeneration
- WG 8: New Clinical Applications: replacement
- WG 9: New Clinical Applications: cancer
- WG 10: Regulatory Science and early Health Technology Assessment & Early Clinical Trials and Refined Translation
- WG 11: Pivotal Clinical Trials and Marketing Authorisation
- WG 12: Post-Trial Follow-up and Data Warehouse & Long-term follow-up
- WG 13: Implementation of new Advanced Therapies into clinical routine
- WG 14: Valuation and innovative reimbursement models for new Advanced Therapies
- WG 15: Ethics

1. Abstract

As of mid-2019, there are more than 1000 ongoing clinical trials on Advanced Therapy Medicinal Products (ATMPs). The global rate of increase in the number of clinical trials with ATMPs in the last 5 years is impressive: +32%. Unfortunately, the same rate in Europe plots a flat line (<2% variation over 5 years).
The reasons for the increasing difference between Europe and the rest of the world are many but above all other reasons is the fragmentation of the European landscape, both on the regulatory side with national and local regulations jeopardizing the field and on the scientific/clinical side where the expertise to navigate this complexity is often lacking.
Here we propose a strategy based on 10 actions (listed below) that requires a joint European effort and that, according to our analysis, could drastically change the current situation. Despite efforts to isolate single roadblocks to be removed, a comprehensive strategy is absolutely needed and none of the proposed 10 actions, implemented in isolation, can really make the difference. The overall strategy is summarized by the Figure 5 and presented in detail in Chapter 5. Listed below are all 10 actions:

A. Horizontal Actions:
    1. Capacity building
    2. Multidisciplinary approach
    3. Data sharing
B. Vertical Actions:
    4. Develop more predictive pre-clinical models
    5. Qualify ATMP platforms
    6. Validate methodologies for non-blind non-randomized clinical trials
    7. Develop infrastructure for Real Word Evidence generation
    8. Create a platform to validate and qualify surrogate endpoints
    9. Co-develop with regulatory authorities “flexible models” for early clinical trials
    10. Support the definition of new models for market access.

2. Deliverable’s description

This document outlines the RESTORE strategy to improve the design of clinical trials on ATMPs. Chapter 3 focuses on the state of the art of clinical research on ATMPs and the EU regulatory framework for those studies. Chapter 4 identifies the current barriers that are slowing the clinical path for ATMPs with a special focus on pivotal/late stage clinical trials.
Chapter 5 details the RESTORE strategy to overcome those barriers with the final aim of having a smoother clinical development path for ATMPs. The last chapter identifies a specific peculiar niche that is still rarely covered by ATMPs developers, i.e. the development and piloting of companion diagnostics suitable for the identification of the patients who would benefit from the access to a specific innovative treatment.

3. Introduction and state of the art

According to the half 2019 report by the Alliance for Regenerative Medicine [1] there were 1.069 clinical trials underway globally by the end of Q2 2019 distributed as in the table below:

Phase	Gene therapy	Gene-modified cell therapy	Cell Therapy	Tissue Engineering	Total	Of which in Europe
Phase I	117	187	49	5	358	52
Phase II	219	207	168	23	617	172
Phase III	30	16	32	16	94	42
Total	366	418	249	44	1069	266

Table 1 – ATMPs' Clinical Tirals per Phase and Approach (source [1])

The great majority of trials are in the oncological field (62%) while the remaining ones are distributed across a wide variety of indications where the relatively most relevant disease groups are cardiovascular (~5%), central nervous system (~6%) and musculoskeletal (~5%) disorders [1].

An additional analysis published by ARM in October 2019 [2] shows impressive data both for the global rate of increase in the number of clinical trials with ATMP in the last 5 years (+32%) and for the flat trend in Europe (<2%). Figure 1 taken from the above-mentioned report summarizes these findings.

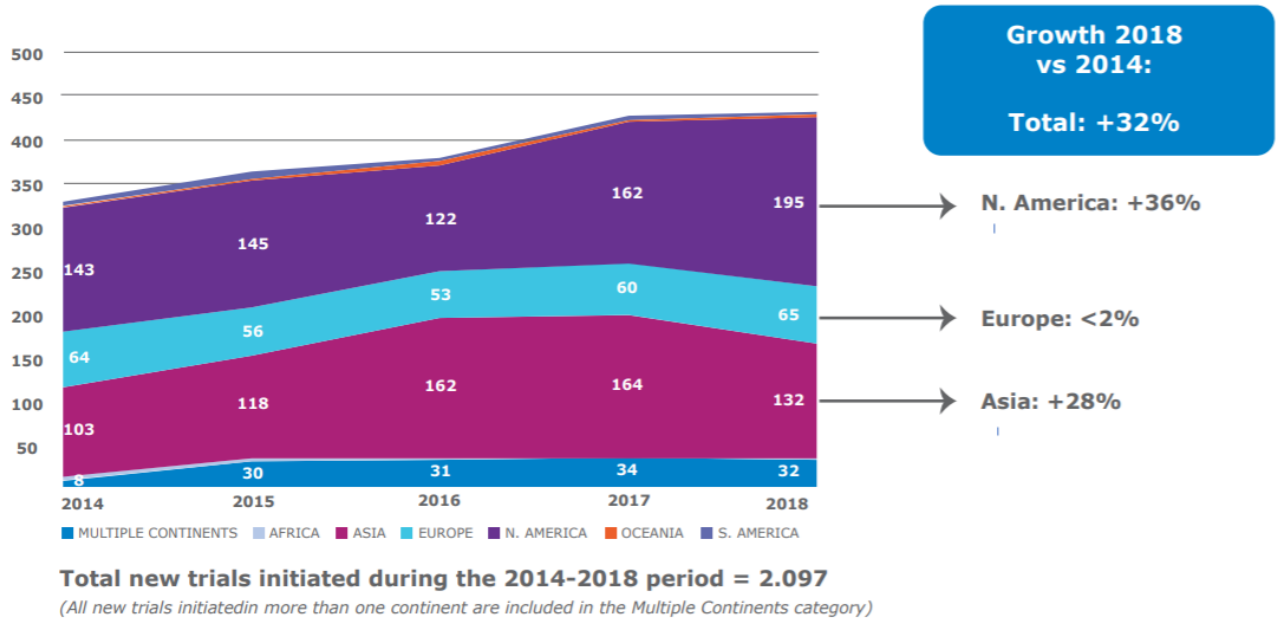

Figure 1 - Clinical Trials Initiated 1 Jan 2014 – 30 June 2019, by Continent and Year (source: [2])

As clearly shown in Figure 1 the sector of ATMPs development is growing quickly globally but Europe is not keeping pace with this global trend. However, despite this global research effort, only a dozen products obtained the marketing authorization in the EU so far and of those, 4 were withdrawn mostly for commercial failure and difficulties in negotiating price and reimbursement scheme in key EU countries [3]. The uncertainty about pricing and reimbursement combined with the high cost of early clinical trials with ATMPs poses additional barriers to a quick and smooth transition from preclinical to clinical phases.

Focusing on Europe, from a regulatory point of view, ATMPs are authorized centrally by the European Medicines Agency (EMA) through a single evaluation and authorization procedure. Despite efforts made by the EMA to provide support to ATMP developers [4], the path for marketing authorization for ATMPs is still very complex as summarized in Table 2, reproduced

from Pellegrini et al. [5]. In the table below, the authors compared the differences in quality requirements for ATMPs that underwent the full marketing authorization process by the EMA and those produced only for investigational use (typically in early phase CTs) or via the so-called Hospital Exemption scheme [3].

Aspects of manufacture	Product with central European Union marketing authorization (e.g., Holoclar)	Other products
Regulatory oversight	Extensively reviewed and approved by European Medicines Agency	National and/or local approval (in most of the cases)
Relationship between product quality and clinical outcome	Consistent product quality correlating with extensive clinical experience	Unlikely to have extensive clinical experience or an established manufacturing process assuring consistent product quality
Manufacturing quality	Full GMP for commercial product	GMP level sufficient for initial clinical use
Manufacturing processes	Process must be validated for consistency	Process validation is not required
Process materials and excipients	Quality and safety must be assured	Local control of selection of materials
Testing	Rigorous testing for critical quality attributes that are correlated with clinical outcome Test procedures must be validated	Extent of testing is less regulated, and not likely to be able to be correlated with significant clinical experience Test procedure validation is not required
Shelf-life	Based on stability studies with multiple batches	Unlikely to have the same level of assurance
Safety from infectious agents	Microbial and viral safety are subject to rigorous assessment	Microbial and viral safety are subject to local assessment
End use	Instructions for use including training to health care professionals approved and validated to maintain quality attributes for clinical efficacy	Instructions for use are locally controlled

Abbreviation: GMP, good manufacturing practice.

Table 2 – Key differences in quality requirements for ATMPs between those with and without marketing authorization in Europe

The difficulties developers encounter to reach the market authorization is further evident if we compare the small number of approved products (14 since 2009) with the number of products classified as ATMPs (282 since 2009) according to the Scientific recommendation on advanced therapy classification reported by the EMA Committee for Advanced Therapies [6]. Moreover, as shown in Figure 2 the approval rate is relatively low, with only 14 products approved out of the 20 that completed the assessment.

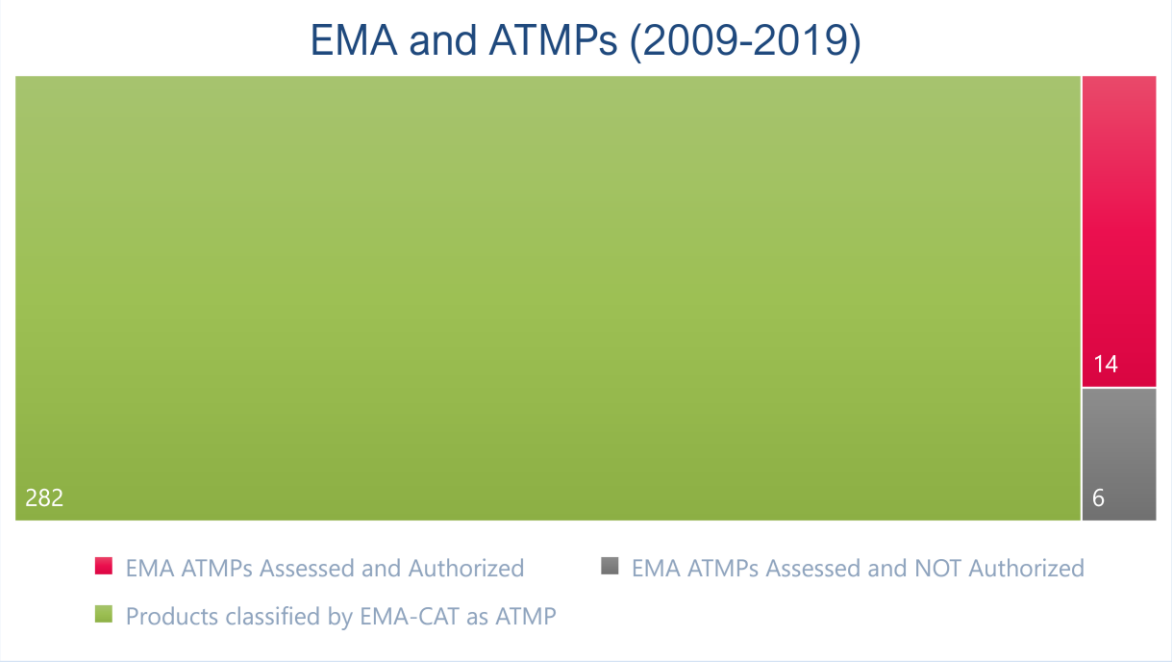

Figure 2 - ATMPs assessed by the European Medicines Agency

In addition to this complex regulatory framework to obtain the centralized market approval, the path to access the different European national health systems is still uncertain as demonstrated

by the high rate of failure in commercialization for 4 out of 14 approved products (30%) [3]. There are several reasons why negotiating reimbursement schemes and prices for ATMPs is so challenging [7] and this uncertainty risks hampering both patients access to effective therapies and return of investment for developers, ultimately leading to sub-optimal development of the whole field of regenerative medicine.
While some of the barriers to access are due to the peculiarity of national/regional regulation of the drug market, there are some common obstacles related with the generation of clinical evidence that could be tackled at a broader level and solutions that can be adopted by developers themselves. This is especially true for the gap between available clinical evidence at the time of launch of the product and the evidence standards required by Health Technology Assessment (HTA) bodies [7].

4. Current barriers and challenges

4.1. According to the literature

There are a number of recently published papers reviewing the barriers to the development of ATMPs which spans from pre-clinical challenges in developing adequate models up to clinical trial and market access [8] [9] [10] [11] [12]. All of those challenges are relevant but according to the survey conducted by ten Ham et al. in 2018 among 68 developers of ATMPs (65% of which were SMEs) the regulatory and manufacturing domains emerged as the most critical for developers. This may be in part due to the high number of SMEs which are likely to have more limited experience and resources on regulatory procedures but it is also true that these same domains are also the most challenging for academia [13]. More than 70% of the developers interviewed by ten Ham et. al. had at least one product in early clinical (phases I–II) and 30% had at least one product in later stages (phase III, registration or commercialization) therefore we can consider those results representative of the landscape of challenges for the clinical and regulatory domains.

REGULATORY AND MANUFACTURING DOMAINS EMERGE AS THE MOST CRITICAL FOR DEVELOPERS

In relation to regulatory challenges, about half of the respondents highlighted the "Country-specific requirements" as the main barrier and 40% reported the preparation of the Regulatory Dossier as the main challenge. This result is also confirmed by ARM [2] whose most recent report stresses the differences in the time requested for the approval of a new clinical trial in the different European countries. As the approval is country-based, the timeline for starting a new clinical trial can vary as much as from less than 30 days to almost one year. Companies rate the "speed of approval" as the second most important criteria when choosing the centre/country where to initiate a new trial [2] and the fragmented European approval landscape combined with the uncertainty on the timeline for approval prevents Europe from being the first choice for many companies.

- ✓ EUROPE IS LOSING GROUND IN THE GLOBAL RACE FOR ATMP DEVELOPMENT NOT KEEPING PACE WITH US AND ASIA
- ✓ THE UNCERTAINTY ON PRICING AND REIMBURSEMENT IS RETAINING THE DEVELOPMENT OF THE SECTOR

Stratifying the results according to the size of the company, about 40% of the large companies highlighted "reimbursement uncertainty" as one of the major barriers they face in ATMP development and commercialization [8].

Moving to a wider view that includes also the challenges faced by non-commercial ATMPs developers, the paper by Lindenberg et al. [9] conducted an extensive systematic review of the literature concluding that the two main barriers are (quoting):

1. inadequate financial support for both the required investments for manufacturing under Good Manufacturing Practice (GMP) and for setting up first pilot series and clinical trials;
2. obtaining the required efficacy results and demonstrating long-term effectiveness data, toward market access and implementation in clinical practice.

As we will see in section 4.3, the experts who joined the RESTORE Working Groups (WGs) on Regulatory Science & Early Clinical Trials, Pivotal Clinical Trials and Marketing Authorisation and Post-Trial Follow-up and Data Warehouse also reported most of the above listed challenges.

4.2. According to a researcher and EMA representative

A broad view of the challenges for ATMP development from both a regulatory and an academic point of view was given by Prof. Gasparini, member of the EMA Committee for Advanced Therapies, during the RESTORE 1st Advanced Therapy Science Meeting held in Berlin on the 25th and 26th of November. Below is a brief summary of the main challenges reported by Prof. Gasparini:

1. In the case of ATMPs developed for rare to ultra-rare indications or, in general, for all the cell and gene therapy products targeting rare mutations even in more common diseases, there is a high risk that the very low number of patients will prevent the development of a second product once the first one reaches the market. This could potentially slow-down innovation and ultimately lead to non-optimal treatment for the patients.
2. There are ethical concerns in inviting a patient to join a clinical study for an innovative ATMP where an approved product already exists and their participation in the trial will prevent the patient from access to the approved product. This is particularly pertinent for example in the case of gene therapy products, which use viral vectors that induce immunity to the vector itself thus preventing the possibility of a second treatment with a different product that uses the same vector.
3. With the increasing use of genome editing and base editing and therefore a deeper and deeper personalization of the products, it may become extremely difficult to run trials with a significant number of patients as every product will be, at least in part, different.
4. Due to the high level of innovation in the field of ATMPs and the rapidly evolving technologies, the lifetime of the products will be shorter than “conventional” drugs. This will cause additional difficulties in setting the price for these therapies, as there will be strong opposing forces driving the decision on reimbursement that will add another layer of complexity on top of the “usual negotiation” between the profit of the company and the sustainability of the health system.

ADDITIONAL CHALLENGES IDENTIFIED BY RESTORE ARE:

- ✓ PREDICTIVE VALUE OF PRE-CLINICAL MODELS
- ✓ CLINICAL TRIAL DESIGN
- ✓ RWE - REAL WORD EVIDENCE - GENERATION

4.3. According to RESTORE WGs

Different RESTORE working groups discussed specific challenges for regulatory rules in early and late clinical trial design. Even though the viewpoint and the focus of each group was different, a strong link among the highlighted barriers can be found and the challenges can be grouped into just a few categories:

1. Pre-clinical models

2. Regulatory
3. Manufacturing
4. Clinical trial design (including biomarkers and clinical endpoints)
5. Real World Evidence (RWE) generation / long-term follow-up data

4.3.1. Pre-clinical models

The limited value of the currently used preclinical models and the complexity of the mode-of-action of most ATMPs has a number of consequences, which affects the step from pre-clinical to clinical phases:

- current paradigms for pharmacodynamics, pharmacokinetics and toxicology studies are often not applicable or relevant
- pre-clinical dose-related safety and efficacy patterns are often not predictive of effects in humans

4.3.2. Regulatory

Despite the specific issues listed below, the general understanding is that, when it comes to the approval of new clinical trials, the regulatory landscape across Europe is too fragmented with a number of different authorities involved at different levels (EU, National, Regional or even hospital level). The consequence of this fragmentation is an extremely complex framework, which requires a strong regulatory expertise to be navigate and is, in general, not attractive for private investors.

Below is the full list of regulatory challenges:

- clinical trials are authorized at national level, which naturally leads to discrepancies and, even where EU guidelines are available, inhomogeneous interpretations and application
- specific expertise is needed for early identification of the optimal regulatory pathway up to marketing authorization to prevent adaption/restart later on in the development phase. This is especially relevant for Tissue engineered products (TEP) where factors such as the extent of cellular manipulation, relationship between cell source and application, and scaffold characteristics may change the regulatory definition of the product and therefore which path to follow.
- Chemistry, Manufacturing & Control (CMC) process and method validation must be repeated in full for any new product, also in the situation where the platform in use was already assessed for an approved product (e.g. gene therapy with the same viral vector and transduction process of an approved product but using a different transgene). The lack of product class characterization induces the regulatory authority to treat any change in a sequence as a completely new product.
- Genetically Modified Organisms (GMOs) legislation was originally intended for the agri-food sector not for medicines. 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.
- GMO authorization is managed by Environmental agencies and not by the competent authority for clinical trials. This leads to a lack of harmonisation between GMO and Clinical Trial Authorization (CTA) requirements;
- Timelines and processes for the approval of new clinical trials with ATMPs vary greatly across Member States.

4.3.3. Manufacturing

Manufacturing of the drug substance and the medicinal product for ATMPs is extremely complex as, a) the product itself is alive and the biology behind it is very complex and not always fully understood, b) product characterization is still not standardized and requires a wide range of not yet fully validated tests and c) especially for autologous products, the source material (cells) has a strong impact on the final product. This complexity makes the scaling-up of manufacturing for late clinical phases as well as the scale-out to other manufacturers a very delicate and expensive endeavour with often-unpredictable outcomes.

As many ATMPs are first developed in academic settings up to First in Human/Early clinical trials, the manufacturing, scale-up and scale-out challenges are further increased by the lack of regulatory expertise in most universities and the lack of industrialized, fully standardized, production processes. This less robust manufacturing and supply chain used in many early clinical trials increases the (micro)heterogeneity of the products, thereby having an impact on the safety and efficacy of what was supposed to be “the same” product.

Bioreactors are an emerging strategy for automated production but the up-scaling from the “manual” production used for early clinical trials to the bioreactors may affect the product quality and therefore the patient response in later trials.

An emerging additional challenge related to manufacturing is the fragmentation of Intellectual Property (IP) of the several different reagents, protocols and cell-lines necessary for the production of the most complex ATMPs. Some of these reagents, protocols and cell-lines are patented by biopharmaceutical companies that may decide not to license them to other developers in order to gain a competitive advantage. If the necessary licenses cannot be obtained under fair and reasonable conditions, then the process needs to be adapted and this can cause delays, uncertainty and additional costs. Therefore, the IP clearance of all processes to ensure the necessary Freedom To Operate (FTO) is a complex task that may need to be performed repeatedly during the development of an ATMP.

4.3.4. Clinical trial design (including biomarkers and clinical endpoints)

Clinical trial design, including the selection of the appropriate biomarkers and clinical endpoints is very challenging in ATMPs for a number of reasons:

- Surrogates endpoints for therapy response are used to obtain conditional approval but payer and HTA bodies often do not recognize surrogate endpoints as strictly correlating with primary outcomes. This leads to a long and difficult negotiation process for the definition of the price and reimbursement scheme.
- There is a need for robust and validated models for mapping molecular target distribution and possible off-target effects especially, but not only, for gene edited products.
- When placebo-controlled trials are not possible, appropriate controls still need to be established (eg. Historical controlled trials). The definition of robust methodologies to run such trials should involve authorities responsible for clinical trial authorization, HTA bodies and payers in order to overcome their scepticism on non-randomized, non-blind controlled trials.
- There is often a lack of markers for patient stratification during late preclinical and early clinical development (phase I/IIa) to prevent unsuccessful (not significant) expensive late clinical trials (de-risking strategy);
- In the case of ATMPs, especially for rare diseases, first-in-human/phase I/IIa studies not only address safety but also include efficacy endpoints. Non-invasive techniques to monitor success at early stages and in a quantitative manner are needed and sometimes missing.

4.3.5. Real World Evidence (RWE) generation / long-term follow-up data

Considering the high costs of most ATMPs and the general lack of strong clinical evidence on their efficacy according to the traditional GRADE scale[1] [14], HTA bodies and payers may raise objections about the cost-efficacy of ATMPs, leading to delayed and slower market access. When the high price is combined with a high budget impact on the health system, payers often look at innovative modalities of reimbursement, the so-called "managed entry agreements". However, these reimbursement models are slow in the undertaking due to the inherent lack of predictability for both Industry and Health Authority, especially when, as is often the case, they rely on real word evidence.

The production of Real word evidence (RWE) is a challenge in itself; however, finding a solution for collecting RWE could contribute to a wider adoption of innovative reimbursement models based on where payment is proportional to the real clinical outcomes on the single patient. This is widely recognized as the way to go to accelerate market access of ATMPs while ensuring the sustainability of the healthcare systems. This is why the experts in WG 12 (Post-Trial Follow-up and Data Warehouse & Long-term follow-up) listed the following challenges related with RWE generation and the collection of long-term follow-up data:

1. Sponsors often lack the capacity for long-term monitoring and compliance with post-marketing obligations. Moreover, industries do not have any actionable legal tool to ensure compliance in data collection and when thinking about potentially curative treatments, there are concerns about the willingness of the patients to still provide their data once "fully cured"
2. Regulatory surveillance in the post-marketing approval phase is necessary to ensure that data are complete, accurate and validated, however, the collection of quality data is complex and expensive
3. Disease registries may be a valuable tool for RWE collection but:
    a. As they are designed as multicentre, investigator-centric studies, this may not be feasible for ultra-rare diseases
    b. Treatment will probably happen in relatively few specialized centres while long term follow-up may be decentralized with the need to train and monitor a wider number of peripheral centres which may input few patients each
    c. Due to their high value, data from this kind of registries is generally not freely accessible to companies, regulatory, HTA bodies and payers.

4.4. Recap of the main challenges

1. Manufacturing has a great impact on both the costs of clinical trials and the efficacy of the product. Scaling-up of the manufacturing from preclinical to phase I and from phase I to phase II and III could by itself be a cause of failure. Moreover, due to the high costs of GMP manufacturing, academic/independent sponsored clinical trials are rarely feasible.
2. The poor predictive power of animal models with respect to ATMP dosing and efficacy in humans leads to a higher failure rate of ATMPs VS small molecules in clinical PoC studies.
3. Clinically viable and relevant biomarkers as well as surrogate endpoints are often lacking or have poor predictive capacity for long-term efficacy. As one of the premises of many ATMPs is that they will be curative, the lack of long-term follow-up data and of good predictive markers for long-term effects is a major issue. Generation of long-term real world evidence is a challenge in itself.
4. The development path of ATMPs is significantly different from the standard drug development path, for example, the number of candidates ATMPs for a specific target that enters the clinical phase is non comparable with the number of molecules entering

[1] According to the GRADE's approach to rating quality of evidence, large & double blind & randomized controlled CTs are top quality evidence while the quality rate of small & non-blind & non-randomized CTs is low.

the same phase in a standard development programme [15]. Moreover, as mentioned, the manufacturing processes imply the use of a number of reagents, cell-lines and procedures that may be covered by IP of third parties, therefore due diligence and FTO analysis should be performed regularly and licenses need to be obtained or processes adjusted. All these differences in the development path and in the sequence of the "de-risking" milestones of a programme, requires a change in the models used to develop new products and to evaluate the risk of investment and the consequent financial needs. Another example is the currently high costs of manufacturing which make clinical PoC much more expensive than the usual small molecule model generating the vicious circle represented in Figure 3.

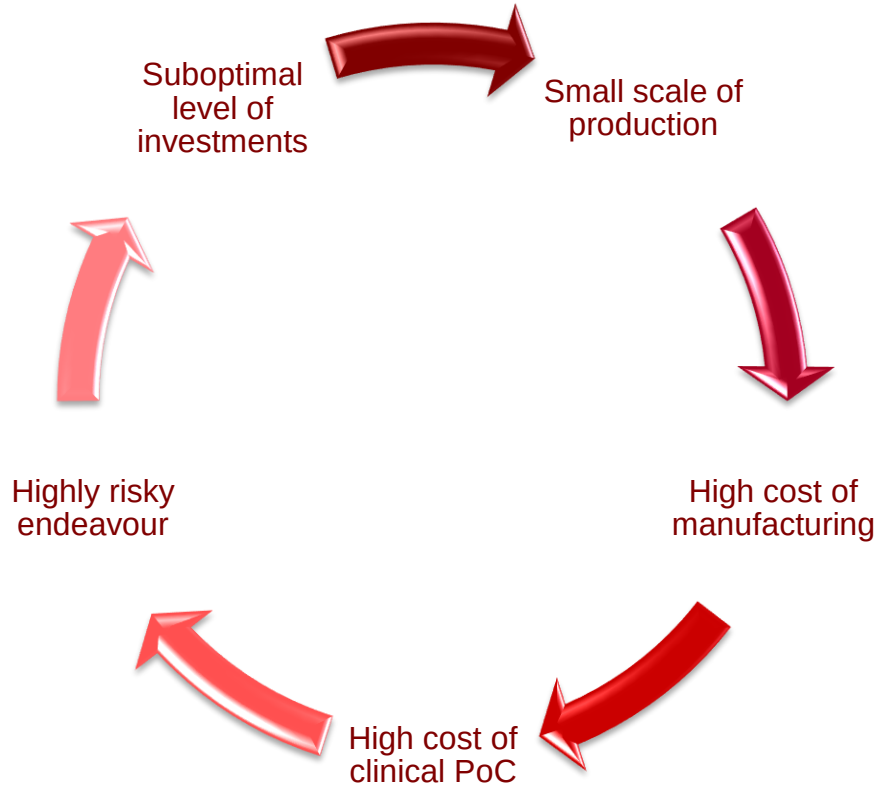

Figure 3 - The vicious circle of high costs for manufacturing investigational ATMPs

5. Double blind randomized clinical trials are rarely an option in the design of clinical trials with ATMPs and the evidence generated in non-blind, non-randomized controlled trials are often not sufficient for HTA bodies and payers
6. The clinical competences to conduct clinical trials with ATMPs are limited and geographically concentrated in a limited number of centers/cities
7. The regulatory competences to navigate the complex path for ATMPs development are also scarce
8. Expectations about pricing and reimbursement affects the investment decision of companies leading to a suboptimal allocation of resources to the sector. The general uncertainty about the marketability of products is suppressing the full exploitation of the potential of the ATMP sector with a number of consequences, among which are the lack of scale in manufacturing and the resulting high production costs. As shown in Figure 4, there are a number of "competing forces" that makes the definition of price and reimbursement schemes for ATMPs particularly complex

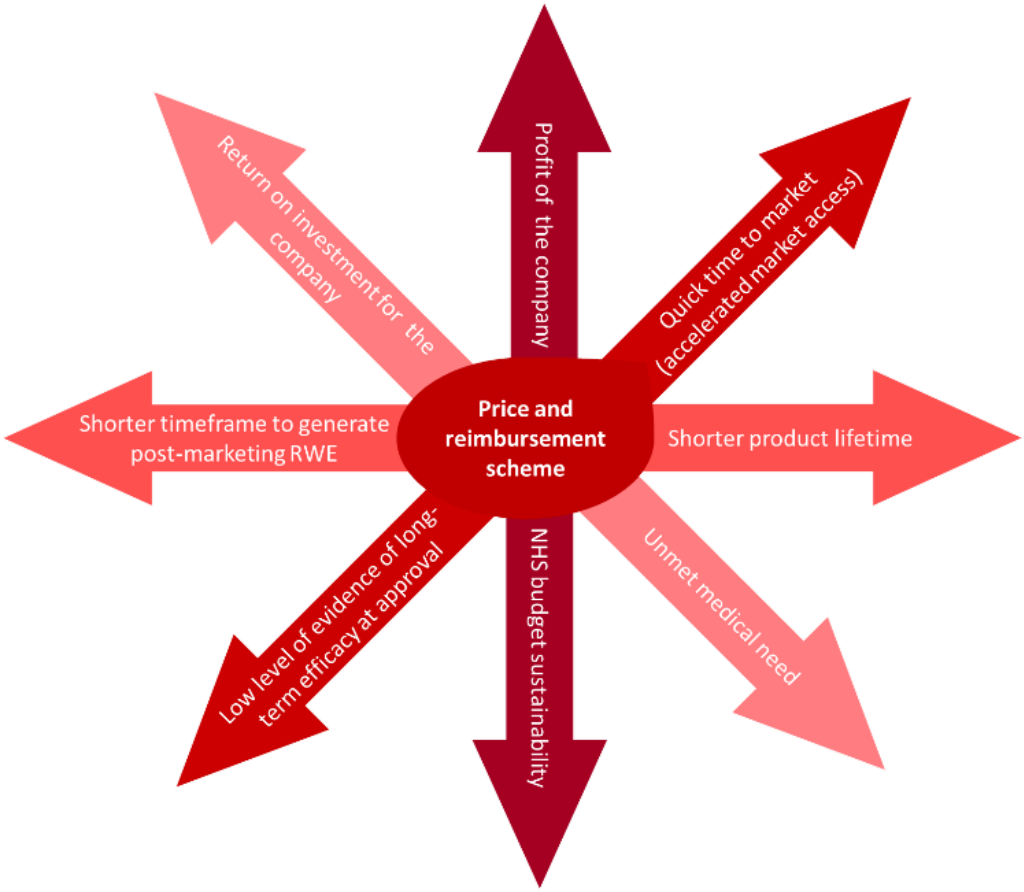

Figure 4 - Competing forces operating on price and reimbursement schemes

9. Despite the harmonization effort by EC and EMA [16] the regulatory framework for the approval of new clinical trials remains fragmented across Europe, with several different local interpretations of EU non-binding guidelines and recommendations and additional national or regional norms. This complexity makes Europe less attractive for the launch of new clinical trials, especially when the study is sponsored by academia or small biotech that may lack the necessary regulatory expertise (see point 7).
10. Risk-based decisions for the approval of new clinical trials and products are not yet widely used in Europe and there is still a high variability among authorities in how to apply this concept.

The ten challenges above may be the most relevant but certainly do not constitute an exhaustive list. It is therefore clear how complex the landscape is and how necessary it is to adopt an integrated approach at a European level. The interconnections among the above listed challenges create a vicious circle that requires a number of actions running in parallel in order to break the cycle. Some of the challenges are global but others are European-specific and, if not appropriately tackled may result in a growing distance between Europe and US/Asia.

5. Future strategies

Before introducing the strategies proposed to overcome the above listed challenges, it is important to agree on the general concept that an integrated, interdisciplinary approach is the only possible way out of the "valley of death" of translating promising preliminary results in approved ATMPs. Quoting a recent, illuminating work by Attico et. al. [17]:
"The analysis of failures and the related "valley of death", which is also described for chemical drugs, has produced a biased description of causes: scientists ascribe setbacks to technicalities and shortage of funding, entrepreneurs blame scientists for insufficient long-term planning and lack of data reproducibility, regulators criticize the lack of accuracy in quality or safety evaluations, patients complain of the absence of therapies for severe diseases, and governments bemoan the increasing health costs. What is the real problem? Is it the sum of all of the above? Most root cause analyses are biased since they describe a single perspective, revealing that cross-fertilization is missing [..]".

Starting with this perspective, the proposed strategy is designed as a matrix where actions tackling a specific challenge (vertical) are supported by cross-cutting programmes (horizontal) that constitute the backbone approach to allow the vertical actions to be really impactful (Figure 5).

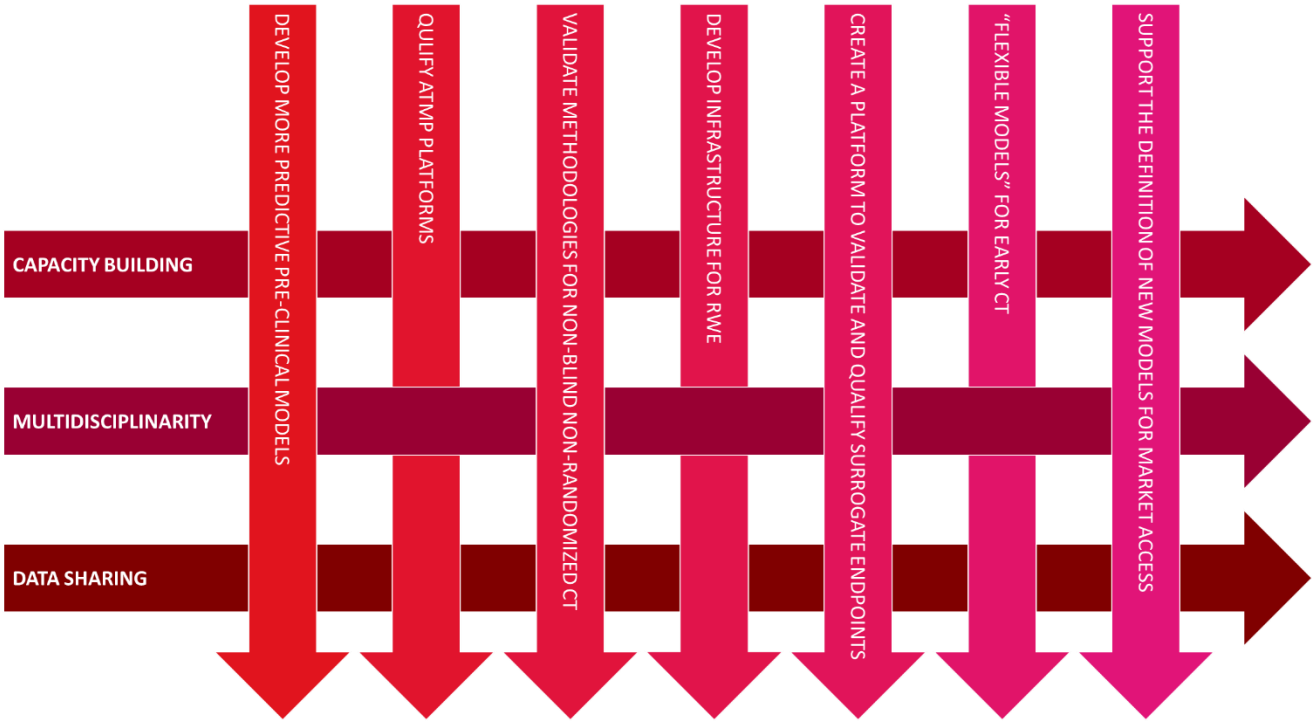

Figure 5 - Overall strategy

In the coming 2 paragraphs, selected horizontal and vertical actions are presented in more details while others are left to the specific deliverables by the relevant WGs (eg. Preclinical models and models for market access).
Some of the challenges identified in the previous chapter are addressed by this strategy only indirectly and this refers specifically to those challenges for which the ideal solution would be a change in the policy/regulatory framework. It is clear that the lack of harmonization of clinical trial approval procedures and of the national implementation of the legislation on GMOs could be better addressed at political/regulatory level and some lobby work in this direction is necessary and could be effective. Nonetheless, the current political framework in the EU Member States may not yet be ready to take further steps in the direction of integration/harmonization and therefore the strategy we propose is designed to work with this fragmented framework.

5.1. Horizontal actions

The three horizontal actions, despite contributing to tackling all the challenges listed in paragraph 4.4, should contribute specifically to:

Challenge 4: new model of drug development specific for ATMPs
Challenge 6: lack of clinical competences to conduct clinical trials with ATMPs
Challenge 7: lack of specific regulatory competences on the development of ATMPs
Challenge 9: fragmented regulatory/authorization landscape
Challenge 10: risk-based decisions on the approval of new clinical trials and products

Capacity building and the enhancement of multidisciplinary approaches for the development of ATMPs are key success factors. Quoting again Attico et. Al. [17]:
"It is clear that specific experts hold leading positions in different phases of development for a new stem cell therapy: scientists in the early phase of research; physicians in clinical trials; and entrepreneurs in the evaluation of opportunities, organization, and funding; as well as public payers and regulators in the reviewing of preclinical and clinical data. They are all involved in the translation and forming the "tower of Babel" and contributing to the valley of death".
Multidisciplinary teams and approaches are clearly necessary to avoid the above mentioned "tower of Babel" but there cannot be effective multidisciplinary teams if any of the necessary specific competences are missing. As shown in section 4.4 there seem to be specific gaps in two fields: regulatory (also due to the complexity of the issues) and clinical application of ATMPs (especially where the products are complex, autologous therapeutics).
The envisaged strategy is a two step approach to target two different groups of stakeholders, both extremely relevant: developers and healthcare providers. The first group will need a full, in depth knowledge of the whole development pathway while the second group should receive training in the administration of the marketed products.
Some tools to facilitate the design of new development programmes in line with the need of ATMPs have been already developed (e.g. the IRDiRC Orphan Drug Development Guidebook) but require wider application. The ideal solution for the developers target group would be to establish "hubs" for the development of ATMPs, which integrate all the necessary competences (science, clinical, regulatory, manufacturing, etc. in a really multidisciplinary approach). They should also integrate Universities, which can formalize the existing implicit knowledge in order to make it transferrable (capacity building). These hubs will also be the ideal solution to deal with the complexity of ensuring the necessary freedom to operate to all and every program. This requires highly skilled professionals to scout for all the necessary licenses and either negotiate them or force researchers to find different solutions. In the long-run, these hubs would ideally develop proprietary intermediate products (e.g. reagents or cell-lines) and adopt fair and open models for their commercialization following the example of Yamanaka reprogramming factors [18].
Qualification of clinical centres to administer ATMPs (either as a centre in clinical trials or as routine administration) is a long, complex and costly process. This process is however necessary to ensure both the smooth implementation of clinical trials and patients' access to treatment once they are available on the market. This qualification process embodies a huge transfer of knowledge, which is currently mostly done by pharmaceutical companies.

Data sharing is a powerful tool to speed-up the development of ATMPs and to reduce the related risks. As demonstrated by the IMI eTOX project, the sharing of existing data on safety and efficacy for several classes of advanced therapies can be made available in a pre-competitive fashion. Data-sharing should span from detailed data on product manufacturing and product characterization allowing the establishment of causative links between clinical outcomes and product characteristics up to collected natural history data and real world evidence that could be used to build control cohorts for the design of new trials.

Data sharing will be especially relevant for manufacturing of common platforms (e.g. viral vectors) to support an easier and more successful scale-up/scale-out. As mentioned, differences in the scale of production means differences in the production processes that results in different quality of the final product. Sharing data on product characterization and linking them with clinical outcomes will allow for the improvement of manufacturing processes reducing the uncertainty and risks of scaling-up/out.

5.2. Vertical actions

The eight vertical actions listed in Figure 5 cannot be launched in isolation, as they are clearly cross-linked one to each other: biomarkers, surrogate endpoints and RWE are strictly linked but these issues are also linked with new model for reimbursement and market access (e.g. managed entry agreements based on RWE).
In this paragraph, we will not discuss the strategy for improving preclinical models as well as the innovative models for market access, pricing and reimbursement as both these issues will be covered by dedicated documents.

To deal with this complexity of cross-linked challenges and actions we propose to launch 3 main platforms:

- A platform to develop clinically viable biomarkers and surrogate endpoints and to validate them by EMA qualification of novel methodologies. The validation of such surrogate endpoints for the regenerative efficacy in various class of pathologies would make the market authorization process easier and likely reduce the amount of post marketing surveillance. This platform should work with a matrix approach, identifying clusters of pathologies and classes of ATMPs in order to identify and validate common safety and efficacy endpoints making them available to the whole community of developers. This platform should necessarily include HTA bodies and payers to be sure that the developed biomarkers and surrogate endpoints are both EMA acceptable but also relevant for price and reimbursement negotiation procedures.
- An infrastructure for RWE data collection dedicated to ATMPs within a European framework that favours data sharing and interoperability. This infrastructure should enhance the quality of evidence collected and be accessible to HTA bodies, payers, developers, researchers, etc. Specific attention should be paid to rare diseases where some infrastructure already exists or are under development but should be integrated into a continuous stream of data collection starting with diseases registries usable for natural history studies up to post-marketing RWE.
- A shared, open data environment allowing the qualification of ATMP platform products in order to reduce the regulatory burden when adopting the same platform for a new indication. This environment should engage regulatory authorities in identifying standards, criteria and models to allows the use the same ATMP platform (e.g. viral vector) for different diseases without repeating the CMC process & method validations every time. The implication of this approach would be both a reduction in costs and time to move from pre-clinical to clinical stage.

5.3. Piloting and validating results

All the actions mentioned in sections 5.1 and 5.2 should be tested and validated in a real environment by running clinical trials at different phases to demonstrate the efficacy of the developed pre-competitive platforms or by reanalyzing data from existing clinical trials to demonstrate the validity of innovative methodologies and surrogate endpoints already in use. This demonstration process should select products that show significant promise and would benefit from Pan European multi-site trials.

When planning those new trials, specific attention should be paid to an additional vertical action that is to validate methodologies to compare the outcomes of the new CTs with treated patient cohorts (historical control design) or relevant natural history studies. As mentioned, the direct comparison with other treatments or even with placebo is not always feasible and the same for blinding or randomization. Regulatory authorities, payers and HTA bodies should be involved in the design of these trials to ensure the acceptability of the results of those studies.

Finally, more "flexible models" for early clinical trials should be tested; by "flexible", we mean for example the possibility to easily introduce improvements in the manufacturing process during the clinical trial execution to immediately incorporate the evidence generated by the trial itself. This flexible approach requires a change in the vision of authorities on CMC procedures that therefore need to be involved since the planning and design of the first in human CT. We believe that, within the frame of a pilot action at EU level and especially for academic sponsored trials, this collaboration can be efficaciously pursued.

6. Final annotation: Companion diagnostics

In considerations of the peculiar characteristics of some ATMPs, in particular gene therapy and gene-modified cell therapy, stratification of patients is a key success factor for the therapy itself. Patient stratification includes both molecular characteristics and clinical phenotype (e.g. disease progression). It is crucial to evaluate the suitability of such complex treatments for patients in order to maximize the benefit to the patient, the outcome for the payer and finally the return for the developers.

The concept of "companion diagnostics", which is becoming the norm for cancer treatment, should be expanded to non-oncological ATMPs where the characterization of the patient is of utmost importance. We therefore recommend running the process for validation of the specific diagnostic tool/procedure in parallel with the development of the therapy. This is even more relevant for those products intended to treat otherwise incurable, life-threatening, progressive diseases in a pre- or pauci-symptomatic phase. In this last case there is an additional challenge: the identification of pre-symptomatic subjects requires a wide screening of the population (i.e. neonatal screening for genetic diseases) therefore, the companion diagnostics should be suitable for that purpose, i.e. a non-invasive, low price test.

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