Health by Advanced Therapies

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Roadmap of WP4
Roadmap of the needs and strategy of the Implementation of new Advanced Therapies

Public

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1. Deliverable's description

This document describes the roadmap of Work Package 4 (WP4) of RESTORE: The Definition of the Needs and Strategy of Implementation and Exploitation for Advanced Therapies. The purpose of this document is to outline the major challenges in the implementation of ATMPs into Clinical routine, obtaining long term follow-up data and identifying new and innovative reimbursement models for Advanced Therapies, and the proposed strategies by which RESTORE aims to address the identified issues.

Objectives

To build a road map to navigate the complex landscape of realising Advanced Therapeutic Medicinal Products (ATMPs) as a standard of care across Europe. We have divided the road map into 3 main areas:

I. Implementation of New Therapies into Clinical Routine
II. Valuation and Innovative Reimbursement Models for new Advanced Therapies
III. Long Term Safety and Efficacy Data

Within these areas, RESTORE proposes strategies to navigate through technical, regulatory and economic roadblocks to support the translation of Advanced Therapies from the laboratory to the clinic.
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 Implementation of new Advanced Therapies.

2. Implementation of new Advanced Therapies into clinical routine

2.1. State of the art

"ATMPs as “living drugs” are different from conventional drugs in their requirements for implementation into clinical routine. This lies in the complexity of the manufacturing, logistics and supply chain processes with multiple steps and high technical demands. In addition, treatment of the patients is extremely complex and requires an experienced multidisciplinary team (clinicians and nurses, geneticists, biologists, regulators, quality experts, pharmacists, etc) that is able to handle the specific requirements of cellular therapies as well as their possible complications (e.g. cytokine release syndrome or neurotoxicity in case of CAR T therapies).

Consequently, we would like to examine the 3 broad stages involved in the routine adoption of these products; the manufacture, supply and clinical adoption. These are each influenced by the phase of development (clinical trial vs licensed supply), the indication and the patient group. In this working group, we also want to tackle some issues that are particularly prevalent for ATMP’s such as short-shelf-life products, ultra-rare orphan products and single centre treatment. Recently, these products have made big advances in development with more products making it through to licensure. With these advances come challenges for the manufacturers, supply chain and the clinical sites delivering these therapies. Within this road map we seek to highlight these challenges and propose to examine the feasibility and effectiveness associated with centralised and distributed models of manufacturing for cell therapy ATMPs.

Currently two general routes for large-scale delivery of ATMPs to patients exist: centralized and decentralized manufacturing.

Centralized manufacturing is illustrated in Fig. 1A: A single facility carries out production and serves to supply ATMPs to a large geographic region. For personalized treatment, this may occur in a discreet region or may require transportation of patient cells across long distances. In contrast, decentralized manufacturing (Fig. 1B) is dependent on regional centres (“hubs”) that are close to the treatment centres and deliver products to their immediate surrounding. Both manufacturing models have benefits, disadvantages and challenges, which are summarised below in Table 1.

Figure 1: Centralised and decentralised manufacture strategies. A) Centralised - Main characteristics: Single facility: cells in -> product out; delivery validated suppliers; controlled process: reduced product variation; higher dependency on integrated supply chain. B) Decentralised - Main characteristics: regional hubs; close to point-of-care; technology transfer of process and analytics; controlled consumables supply chain.

Table 1. Centralized and decentralized models for ATMP manufacture and clinical adoption (Haddock et al., 2017; Harrison *et al*., 2018; Lyer *et al*, 2018; Rutherford *et al*, 2017).	Centralized Model	Decentralized Model
Manufacturing	Single facility carries out production	Multiple regional hubs close to treatment centres & deliver to immediate area
Logistics demand	High due to shipment of product over large geographical regions	High – complex supply chain (donation sites, multiple points of manufacture and distribution)
Process control	High	Lower - multiple production sites add complexity to process control to ensure a standardized output of cellular products.
Quality control	High	Complex (as above)
Risk to product variation	Lower due to single site manufacture, intrinsic variability of starting material/process	Higher (as above) – multiple sites and operators add to intrinsic variability
Tech transfer requirements	Low	High – with respect to manufacture and analytics across all sites
Overheads	Lower (due to single site) but require larger space	High – replication of equipment at multiple sites
Geographical distribution range	Supplies to a large region	Small (dependent on hub size)
Specialist resource requirements	Lower	High – production in multiple hubs requires the duplication of specialist resource across all sites
Suitable for product types	Autologous and allogeneic cell products that are not sensitive to cryopreservation and/or transportation	Autologous and allogeneic cell products with limited stability and/or maximum efficacy requirements

To date, whilst decentralised manufacturing has been widely discussed, it has not been systematically evaluated for feasibility, practicality and cost in the context of a busy healthcare environment in comparison with centralised manufacturing models.

As is evident from Table 1, the nature and complexity of cell therapy production means there is a trade-off between the costs of manufacture and the costs of the supply chain. Hence, a centralised manufacturing strategy (up-scaling) is best suited to high complexity and costly manufacturing, especially where the supply chain costs are low (Fig 2A). However, the greater the complexity of the incoming and outgoing supply chain processes (e.g. for labile/short-shelf life product), the more distributed the physical supply chain could be, assuming the manufacture of the product can be relatively easily standardised and out scale (simple e.g. automated manufacture process). Hence, such products should benefit from a distributed decentralized manufacturing model (Fig.2B) (Rutherford *et al.*, 2017).

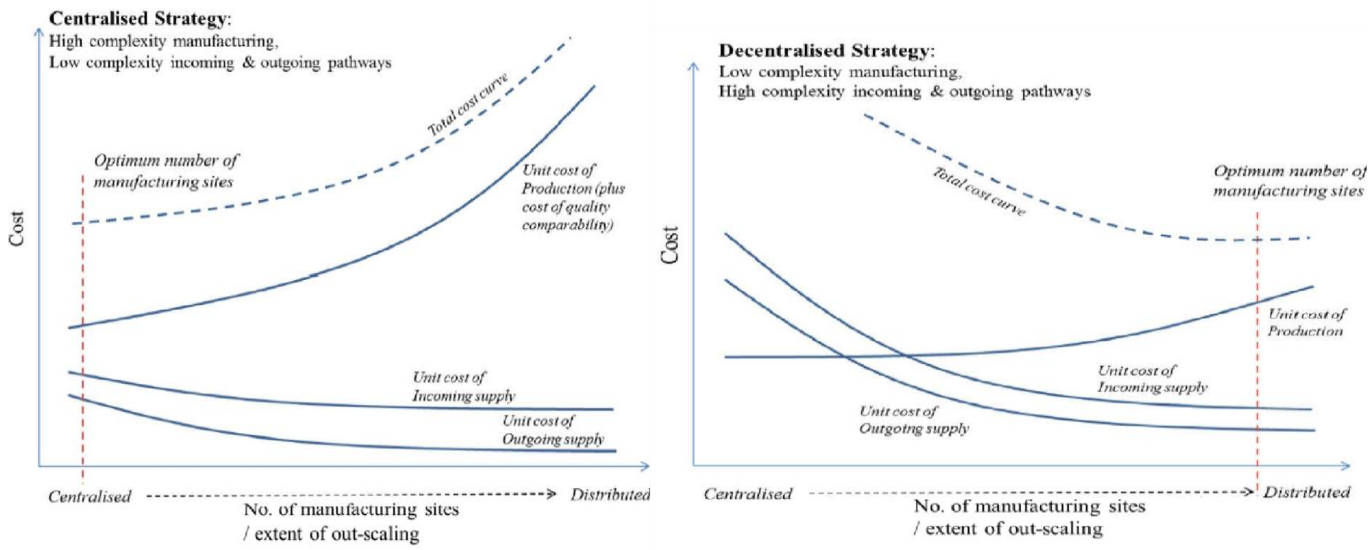

Figure 2: Manufacturing cost/ complexity relationship. A) Centralised and B) Decentralised

In practice, **centralised manufacturing** has already been implemented by pharmaceutical companies for a number of the licensed ATMPs such as Strimvelis (Orchard), Zalmoxis (Molmed), Holoclar (Chiesi), Kymriah (Novartis) or Yescarta (Gilead). This model is in keeping with routine pharmaceutics and as such is tried and tested, however for ATMPs there are some points of criticism associated with this model, such as the high costs that are claimed by the suppliers and the dependency on a single supplier. For the medical centres, there is a lack of transparency with respect to details of the cell processing by the manufacturer. Currently, this strategy is the model of choice for autologous products and it might be the option of choice for **off-the-shelf (allogeneic) cell products** when many doses with long shelf-lives can be produced for a large number of patients (Harrison et al., 2018). In this case, the cost/benefit ratio will be advantageous in comparison to decentralized manufacturing of off-the-shelf ATMPs (Harrison *et al*., 2019).

Decentralised manufacturing has not been established in practice so far as clinical application of cellular therapies is still in its infancy and most clinical trials are still in their early stages. Despite the challenges with batch reproducibility, there is considerable interest in this model, which might be best suited for **autologous cell products** and applicable to pharmaceutical approaches as well as smaller biotech companies and importantly, to specialized hospitals that are producing ATMPs at POC. However, in order to avoid product variations each hub must be able to deliver equivalent ATMPs

regardless of location or operators. This may be best ensured by use of integrated management and automated systems (Harrison et al., 2018; Kaiser *et al*., 2016).

2.2 Major challenges and roadblocks to be addressed

Regardless of manufacture model the following challenges need to be addressed to facilitate broad clinical implementation of ATMPs:

A. Specialist facilities and knowledge at clinical sites – from initial treatment decisions, apheresis (where required), pharmacy, treatment, follow-up, JACIE accreditation, etc.

B. Seamless and robust supply chains and logistics covering starting materials, consumables, products and samples

C. Complexity of treatment procedures and requirement for long term follow-up – patient and physician engagement

D. Market approval – WG Pivotal clinical trials and market authorisation

E. Complex administrative and financial processes linked to treatment of ATMPs, novel reimbursement models will require payers to adopt new processes – WG Valuation and innovative reimbursement models for new Advanced Therapies

F. Additional requirements for ultra-rare diseases where small numbers of patients may have to be relocated to specialist centres for extended periods of time.

2. 3 Overall Goals

Our goal is to enable the spread of Advanced Therapies (ATMPs) for a range of broad applications. By achieving this, RESTORE would be serving the needs of thousands of patients, democratising ATMP manufacture, smoothing clinical adoption and enabling broad access to these highly promising treatments. To ensure this vision becomes a reality, commercially viable infrastructures and manufacturing models must be established that facilitate advanced therapies (including local hospitals e.g. in rural areas that do not possess specialized GMP facilities). We will also need to develop and implement a training system that will ensure the expertise required to manufacture, deliver and administer these innovative treatments, which are now available.

2. 4 Scope- Where can RESTORE make a difference

Centres of excellence (Hubs) – addressing challenges A, D, E and F

Clinical centres of excellence "hubs" should provide both strong research and translational capabilities and include both point of care and manufacturing capabilities. Overall, a requirements standard should be set for all these clinical facilities, e.g. like JACIE standards (Joint Accreditation Committee ISCT-Europe & EBMT) establishing the minimum criteria that the clinical centres must fulfil. Establishing a network of Hubs, with individual specialisms, but alignment on standards around procurement, processing, delivery of products, training, efficient long-term follow up and streamlined patient access would be the most efficient use of resources and enable the widest range of therapeutic options to be made available.

The clinical centres will address research and routine delivery requirements for advanced therapies including procurement and processing of starting materials and products, pharmacy, cell labs, clinical infrastructure and service design in a collaboration between healthcare organisations, ATMP developers, service industry partners and academia. They will play a key role in developing therapy and manufacturing guidelines, developing and implementing training across the supply chain, standardisation of processes and procedures as well as overall service design, delivery and integration into the wider eco-system. Training at all levels and steps along the process will be key to the success of broader implementation of ATMPs.

The manufacturing facility will provide ATMPs with consistent, proven quality for internal use and for external, local hospitals (Fig. 3). This will require standardized technology transfer including logistics, supply chains, quality management systems, staff training, patient counselling, advice on reimbursement matters etc. – not only within the centres-of-excellence, but also involving the local hospitals. Moreover, the centre of excellence will need strong research capabilities to use the expertise from established Advanced Therapies for further improvement and for extension to other new indications.

Figure 3: Centre of Excellence. For internal use, the "hubs" will serve for procurement of the biological material, ATMP manufacturing and patient treatment. Moreover, they will transfer ATMPs, technology, know-how and standards to local hospitals that by themselves don't provide manufacturing infrastructures.

In summary, one of the challenges for RESTORE for broad clinical implementation of Advanced Therapies will be to elaborate a concept with general specifications and requirements for European Infrastructure of centres of excellence. In a second step, the specific therapeutic conditions to handle different disease entities will have to be integrated (e.g., regenerative medicine will have other requirements than immunotherapeutic therapies).

Seamless supply chain and logistics – addressing challenge B, D and E

Provision of seamless supply chains and corresponding logistics that apply to both centralised and decentralised manufacturing is crucial. Requirements are outlined in Figure 4. The concept only gives an outline of the complexity involved in supply and logistics. In real life, the requirements are even more challenging and require significant changes to current strategies and infrastructure. Hence, for implementation into clinical routine standardized processes have to be developed to help manufacturers to solve these issues. The requirement for specialised handling of the products at

POC cannot be overlooked; this can be improved by the use of controlled equipment and thorough training and support of staff.

Figure 4: Seamless supply chains and logistics. Main characteristics: Track and trace, supply logistics, remote monitoring and streamlined IPC/QC across sites.

One solution to serve this need could be provision of blueprints e.g. for infrastructure, reagents, devices, QC, monitoring etc. Also, the whole administrative path within the hospital from the order for the ATMP drug placement has to be integrated and mapped to secure full ATMP cost reimbursement after patient treatment. Additionally, specialized handling of ATMPs in hospitals is often required (for instance, cell thawing, resuspension, etc.) and failure to provide appropriate instruction, train and support properly the staff has resulted in large variability in ATMP performance between centres participating in clinical trials. This is a significant issue that has made some products/companies go bust.

Complexity of treatment procedures – addressing challenge C

It is not only the complexity of manufacturing but also structural issues and the complexity of treatment protocols (including control of possible side-effects) that are limiting roll-out of ATMPs from early experimental stages to clinical routine. Patient treatment may be extremely complex for cell- or tissue-based medicinal products. All hospital actors (clinicians, pharmacists, cell therapy staff and administration) have to be familiar with the different treatment guidelines and with management of the possible complications associated to the specific disease and with the ATMP administration (e.g. cytokine release syndrome or neurotoxicity in CAR T therapies). Guidelines for training, similar to the one applied for stem cells transplants, should be delivered. The definition of the amount of training and the resources for testing the quality of the learning should be defined.

For many of these ATMPs tested in clinical trials, including the ones that are potentially curative, there still only exist limited long-term safety and efficacy data. Thus, it is essential to continue the follow-up in the long term and to provide conditions that favour patient compliance for collecting these data. Also, the concept of “ATMP-treated patients registries” has to be taken into consideration.

Administration of these therapies requires engaging both, the patient and the referring physician, and to educate them on this new treatment perspective. Even though it might be transformative and curative, emotional difficulties should not be overlooked.

5-10 YEARS: Execution phase

Execution phase: building-up an European infrastructure of ATMP hubs

a. Identification/appointment of potential clinical centres of excellence

b. implementation of selected cellular therapy trials within centres of excellence network

2.5 Expected key deliverables for 4-5 years

The overarching deliverable will be setting up systems within the EU that will allow manufacture, distribution and administration of ATMP's across a wide range of therapeutic areas. This will involve:

4-5 YEARS: Concept phase

1. Establishing a **European Network for implementation of ATMPs into clinical routine**: Identification of most important stakeholders e.g. research, clinics, potential manufacturing hubs, industry, patients (national and European patient associations), health care providers, regulatory authorities (for drug and for cell-based procedures), payers, regional and national health technology assessment (HTA) bodies …
    a. Involvement of already existing networks, projects, initiatives
2. Concept for a **European infrastructure / ecosystem of centres of excellence**
    a. **Assessment of requirements** for ATMP manufacturers, researchers and clinicians for late phase clinical trials and entry into market
    b. Definition of **format of potential hubs** (will vary e.g. according to indication, country-specific requirements, cell product type (e.g. personalized vs. off-the-shelf), market …)
    c. Definition at EU level of the minimum set of criteria - by product type - that the collection and administration centres must fulfil to qualify according to the applicable laws
3. Blueprints and guidance to facilitate **approval and market access** of ATMPs for:
    a. Regulatory issues
    b. Inclusion into therapy guidelines, earlier lines of defence …
    c. marketing authorization support, conditional MA, hospital exemptions …
    d. seamless supply chains
    e. reimbursement models

Literature

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3. Valuation and innovative reimbursement models for new Advanced Therapies

3.1 State of the art

3.2 Major challenges and roadblocks to be addressed

- High manufacturing, logistics and supply chain costs demand high reimbursed prices for commercial viability
- High reimbursed prices require demonstration of significant magnitude of incremental benefits over existing therapeutic alternatives
- High administration, patient management and infrastructure costs as well as clinical centres qualification and training costs (all these costs are additional to therapy acquisition costs)
- High reimbursed prices and delivery costs raise affordability challenges for payers and healthcare systems
- Clinical feasibility constraints with ATMPs often result in evidence available at time of launch being of lower quality than what HTA bodies and payers are accustomed to (with small molecules and biologics currently)
- HTA frameworks not flexible enough to account for ATMP idiosyncrasies with respect to available data at launch, accounting for long term benefits (i.e. efficacy, safety, cost avoidance in the long term) and curative potential
- Innovative pricing schemes widely discussed as a tool for dealing with uncertainty and affordability challenges but not always implemented due to high administrative burden, legal/accountancy constraints and also impact on manufacturer cash flow
- Lack of sufficient data collection infrastructure and tools to enable long-term data collection for the purpose of reimbursement
- Lack of clear valuation methodologies to enable strategic steering and go/no go decision making during early ATMP development

3.3 Overall Goals

- Improve the methodological frameworks used in Health Technology Assessments (HTAs) to capture the true value of ATMPs
- Manage payers' affordability concerns without restricting patient numbers
- Reduce barriers to implementing outcomes-based reimbursement schemes
- Increase the harmonisation between regulatory and HTA processes
- Develop tools to assist in valuing ATMPs at the different stages of development
- Develop tools to mitigate common challenges in evidence generation to support HTA
- Support a single Joint Clinical Assessment at European Level (in line with the EU Commission Proposal on Health Technology Assessment Regulation 31 January 2018)

3.4 Scope- Where can RESTORE make a difference

- Improve the methodological frameworks used in Health Technology Assessments (HTAs) to recognise the true value of ATMPs

  - Assess: Conduct evidence reviews of ATMP HTA decisions across Major European Healthcare Markets (MEHM), and identify key limitations
  - Optimise: Liaise with Health Economics and Outcomes Research (HEOR) experts and centres of excellence to critically appraise the HTA methodologies used for reimbursement purposes in MEHMs
    - Identify methodological limitations and suggest strategies for improvement
  - Manage change: Engage with HTA bodies and umbrella patient organisations to raise awareness and promote the implementation of methodological improvements
    - Gather feedback from HTA bodies, umbrella patient organisations and industry stakeholders on the strategies for improvement

- Manage payers' affordability concerns without restricting patient numbers
  - Assess: Current payer management of budget impact concerns related to ATMPs through secondary and primary research with payer bodies in MEHMs
    - Identify implicit/explicit budget impact thresholds
    - Explore and identify strategies to minimise budget impact challenges; consider alternative models for reimbursement, with payment over time as milestones are met, such as performance-based reimbursement {PBR} schemes
  - Optimise: Raise awareness around strategies to minimise affordability challenges through
    - A series of workshops with European payer and industry stakeholders to explore the strategies identified above
    - Development of a white paper outlining potential solutions based on payer body feedback
  - Manage change: Engage with payer bodies in MEHMs to enable the implementation of these strategies

- Reduce barriers to implementing performance-based reimbursement (PBR) schemes
  - Assess: Barriers to implementing performance-based reimbursement (PBR) schemes from the perspective of payers and manufacturers
    - How data collection infrastructure can be optimised to support longer term regulatory, reimbursement and product lifecycle data requirements across countries and therapy areas
      - Analysis of national vs. cross-country infrastructure
      - Assess the feasibility of upgrading existing registries to the functionality needed for PBR
      - Assess the feasibility of an information system that integrates information from multiple sources like disease specific registries, non-disease specific databases, electronic patient records etc, to generate the information needed for PBR
      - Assess the feasibility of a novel cross-therapy area and cross-country data collection infrastructure
    - Assess legal and accounting constraints and potential solutions
    - Assess third party finance solutions to overcome manufacturers concerns over cash flow challenges due to PBR
  - Optimise: Identify strategies to increase adoption of PBR schemes through a series of workshops with European payer, umbrella patient organisations and industry stakeholders, and relevant expert third parties, to identify priority areas for implementing change
  - Manage change: Engage with payers, umbrella patient organisations and industry representatives to support the implementation of a cross-country PBR pilot scheme

- Increase the harmonisation between regulatory and HTA processes
    - Assess: Liaise with HEOR and regulatory experts / centres of excellence to identify commonalities and differences between regulatory and HTA frameworks in MEHMs
    - Optimise: Identify and communicate opportunities to harmonise regulatory and HTA efforts through
        - A series of workshops with EMA and EUnetHTA representatives including umbrella patient organisations to explore the opportunities identified above, and define potential priority areas for implementing change
        - Development of a white paper outlining potential solutions based on workshop feedback
    - Manage change: Support EMA and EUnetHTA in implementing pilot projects in priority area(s) identified

- Develop tools to assist in valuation of ATMPs at the different stages of development
    - Assess: Liaise with HEOR experts / centres of excellence to map the methodological tools available to value ATMP assets at different levels of developmental maturity, depending on the availability of (clinical) data, including
        - Indication prioritisation (early/pre-clinical stage)
        - Identification of efficacy thresholds required for commercial viability (early clinical/pre-pivotal stage)
        - Development of cost-utility and budget impact analyses models that capture the true value of ATMPs (later stage, approaching launch)
    - Optimise: Write white papers detailing preferred methodological tools for the different development stages

- Develop tools to mitigate common challenges in evidence generation to support HTA
    - Assess: Liaise with HEOR experts / centres of excellence to map the methodological tools available to reduce decision uncertainty in HTAs, including cases where, e.g.
        - Long-term value claims are made extending well beyond the trial observation period
        - There is only historical control data to be used for comparisons and:
            - The natural history of disease not well known
            - The patient population is heterogeneous
        - Small trial size creates a challenge to statistical significance
        - Trials including surrogate rather than hard outcomes
        - There are no (obvious) comparator treatments
        - There are no measures of outcome available (e.g. in certain very rare conditions, where these need to be developed)
    - Optimise: Identify the preferred methodological approaches (from an HTA perspective) for tackling the evidence-generation/decision uncertainty challenges mapped out above through
        - A series of workshops with EUnetHTA representatives to explore the methodological tools identified above
        - Define preferred methodological solutions to the challenges identified, and how these may differ across different MEHMs
    - Manage change: Develop methodological guidance documents on the most efficient evidence generation processes during clinical development (including clinical trial data, modelled data, other)
    -

3.5 Expected key deliverables for 4-5 years

In the table below, we outline a three-stage approach on how we can approach these goals over the next five to 10 years: first through assessing environment, then by identifying ways for optimisation and finally by managing change.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 5+
Goals	Assess		Optimise		Manage change	
A	Assess the appropriateness of existing HTA methodological frameworks		Identify limitations and suggest areas for methods research and optimisation		Engage with HTA bodies to enable the implementation of methodological improvements	
B	Current payer management of budget impact concerns related to ATMPs		Identify strategies and raise awareness around how to minimise challenges		Engage with payer bodies to enable the implementation of these strategies	
C	Barriers to implementing performance-based pricing (PBR) schemes		Identify strategies to increase adoption of PBR schemes		Engage with payer bodies, industry stakeholders and relevant third parties to enable the implementation of these strategies	
D	Identify commonalities and differences between regulatory and HTA frameworks		Identify and communicate opportunities to harmonise regulatory and HTA efforts		Facilitate the harmonisation between market authorisation and HTA for ATMPs	
E	Identify optimal methodological approaches to assessing the value of ATMPs at different developmental stages		White papers on: *early stage (pre-clinical), mid-stage (pre-pivotal) and late-stage (pre-launch) ATMP valuation*			
F	Identify common challenges in generating data to support HTA and reimbursement		Identify preferred methodological approaches (from an HTA perspective) for tackling the common evidence-generation challenges		Develop guidance documents on the most efficient evidence generation processes during clinical development	

Long term safety and efficacy data and Patient Registry

EMA published guidelines for LTFU of patients administered with ATMP,

f. EMEA/CHMP Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008) [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500006326.pdf.].
g. EMEA/CHMP/GTWP/60436/2007 - Guideline on follow-up of patients administered with gene therapy medicinal products [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf].

- EMA may require further PASS or PAES monitoring requirements
- The European Medicines Agency's Initiative for Patient Registries aims to optimise and facilitate the use of patient registries for benefit-risk evaluations of medicinal products.

- EMA has provided qualification opinions on two registries, the European Cystic Fibrosis Society (ECFS) patient registry and the Cellular Therapy module of the European Blood and Marrow Transplant (EBMT) registry, describing the contexts in which EMA considers the use of registry data suitable

- Several patient registries exist

4.1 Major challenges and roadblocks

- Patient compliance in LTFU studies and collection of data
- Registry are design as multicentre, investigator-centric study, which is not feasible for ultra-rare disease
- Registries design may be not suitable for ATMP
- Data may not be complete, accurate, and validated
  Due to their high value, data from these registries is generally not accessible to companies / regulatory/HTA bodies / payers

4.2 Overall Goals

To have many disease / product registries that can act as reliable source of data for regulatory purposes and payers

4.3 Scope- Where can RESTORE make a difference

Long-term vision (8-10 years):

- Have suitable registry to be used as a source to compare NH data and LTFU data for one or more unmet medical needs in European community
- Have key ATMP related registries linked into a network with reimbursement data incorporated

Short-term (next 3-5 years)

- Increase patient compliance and data collection in LTFU studies and registries
- Use of digital tools and artificial Intelligence to collect data from remote
- Define a patient centric model registry
- Creation of a common vocabulary to meet the requirements
- Create a network connection among different registries
- Set up new registries for regulatory purposes for specific diseases
- Define a process to allow regulators and payers to have access to registry data to monitor ATMP long term efficacy performance

4.4 Expected key deliverable for 4-5 years

- Define criteria for a registry and its purposes (natural history, safety data, efficacy data, reimbursement)
- Mapping existing registries and their data reliability and compliance with ethical and privacy requirements
- Connect existing registries in a network