Health by Advanced Therapies

D 3.3 Strategy paper on early Health-Technology Assessment tools for Advanced Therapies
D4.4 Strategy paper on Health Economics & Reimbursement

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Due to the close and interlinked nature of the subject of the deliverables D3.3 and D4.4, we have prepared a joint document for these two deliverables. Section 1 pertains to D3.3. Section 2 pertains to D4.4.

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Section2. D4.4 Strategy paper on Health Economics & Reimbursement

Section1. D3.3 Strategy paper on early Health-Technology Assessment tools for Advanced Therapies

1. Deliverable's description

Advanced Therapy Medicinal Products (ATMPs) can be defined as a new class of medical interventions and can potentially be used to treat a variety of human health issues, including neurodegenerative diseases (such as Huntington's and Parkinson's diseases), inherited diseases (such as immunodeficiency syndromes), autoimmune diseases (such as diabetes, multiple sclerosis and rheumatoid arthritis) and cancers (such as leukaemia and melanoma). ATMPs are desigend out of composite biomaterials based on e.g. somatic cells, genes or tissues. The variability is quite numerous, including cell suspensions, viral vectors, plasmid DNA or mRNA, engineered tissues and combinations thereof. The development of new biomaterials and composite products is particularly important for severe, rare, or chronic diseases where conventional approaches have proven to be inadequate or where there is room to improve particular treatment strategies (e.g. administering the genetic information encoding the protein rather than the protein itself).

Universities are a major driver and force in this investigational field. Most ATMPs are initially developed by universities and more than half of the clinical studies with ATMPs in Europe are sponsored by universities. However, the number of patients treated with specific ATMPs still is very low.

ATMPs are centrally regulated at the European level through Regulation No. 1394/2007 of the European Parliament and of the Council of 13th November 2007 on ATMPs and amending Directive 2001/83/EC and Regulation No. 726/2004. A Marketing Authorisation (MA) is needed for ATMPs to be commercially available. The European Medicines Agency's Committee for Medicinal Products for Human Use makes a recommendation for MA to the European Commission which makes the final decision. Some examples of ATMPs, which are currently commercially available, are Holoclar, which uses human corneal epithelial cells to treat the degeneration of corneal tissue resulting from chemical or physical burns to the eye, and Kymriah and Yescarta, where lymphocytes of patients with leukaemia are genetically modified to recognize the patient's own cancer cells and destroy them (see also figure 1).

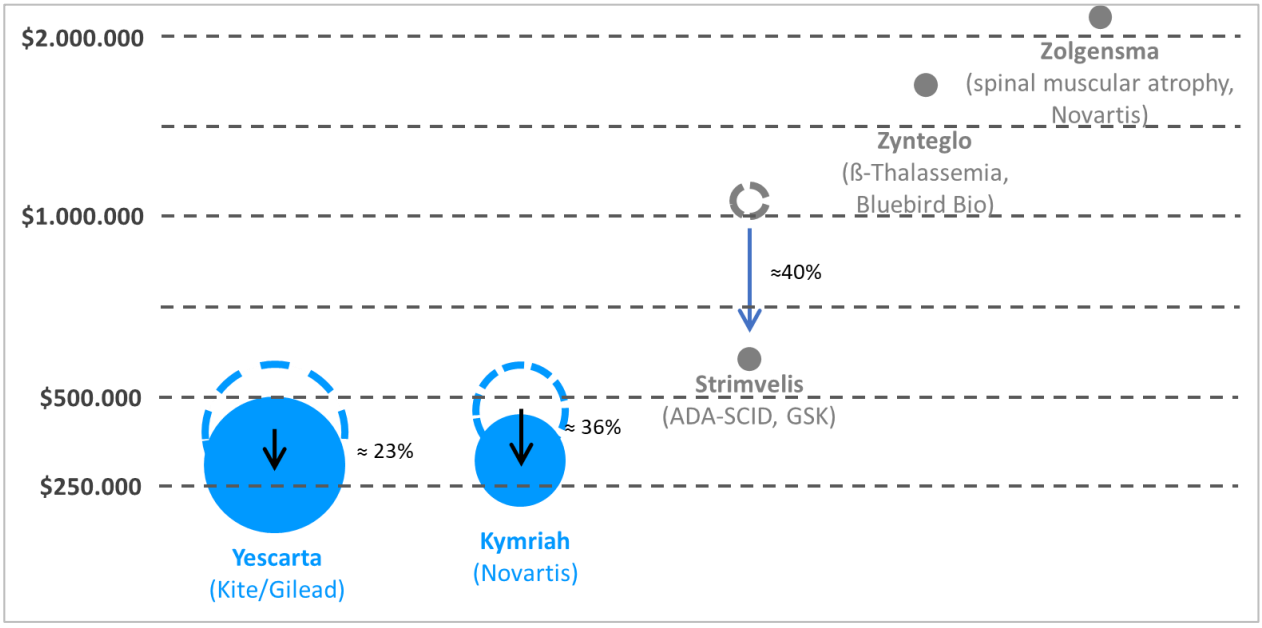

Figure 1: Pricing of current gene therapies. Costs for therapeutic cell products are illustrated in the figure as well as relative market sizes (indicated by the different contents of the circles). CAR T cell products (in blue) are compared to other gene therapy products (Strimvelis, Zynteglo, Zolgensma; in grey). Dashed circles indicate the initial prices of Yescarta, Kymriah and Strimvelis; arrows and percentages indicate drops in market prices in Germany. Initially in 2018, Novartis charged USD 475,000 for Kymriah and Gilead UDS 373,000 for Yescarta. Since then, prices have dropped significantly, i.e. in Germany to USD 304,000 for Kymriah and USD 311,000 for Yescarta (Siegmund-Schultze, 2019) – which equals pricing reductions by 36% respectively 23%.

ATMPs are very different to conventional medicines, often having complex manufacturing processes, orphan indications and tailored production, and are therefore often seen as products with a low commercial value and/or a high commercial risk. As of May 2019, 14 ATMPs have been granted a MA for the European Economic Area (EEA), however, four of them already have been withdrawn from the market for a variety of reasons. An alternative route for patient access in Europe is through the hospital exemption, which allows the use of ATMPs under the supervision of a medical practitioner, on a non-routine basis, and in restricted circumstances, in a single member state. As already described before, universities are a major player in the ATMP field. Most ATMP products are initially developed by universities and more than half of the clinical studies with ATMPs in Europe are sponsored by universities. In part, this is because university medical centers have the necessary disease-specific expertise, the capacity for innovative research and direct access to donor and patient material. Universities dominate early stage (phase I/II) clinical research, while industry is more involved in late stage (phase III/IV) clinical development.

In this context described, worldwide ATMPs are beginning more and more to reach biomedical markets, and it exists an open question about their importance for patients and how insurances/healthcare systems should reimburse for them.

In order to foster prospective marketing authorizations of ATMPs it will be discussed in this document:

i) if current health technology assessment (HTA) methodology used for the assessment of ATMPs might not be efficient enough and

ii) how it could be improved in the framework of RESTORE.

2. State of the Art

Health technology assessment (HTA) is a widespread interdisciplinary instrument that analytically examines the clinical efficacy and effectiveness, technical performance, safety, cost-effectiveness, organizational implications, social consequences, legal and ethical considerations.

With the goal to harmonize the HTA process, working procedures have been developed since many years. Currently, a set of 15 principles is the base in assessing existing or establishing new HTA activities. These principles describe and discuss elements of good practice in developing the structure and remit of HTA organizations, the methods of and processes for conducting HTA, and the use of HTA in decision-making.

The EuNetHTA (European Network of HTA) has developed an agenda to enable transparent structures, processes and standards for handling evidence and information across various forms of HTAs, economic evaluations, and other forms of assessments of the value of interventions across institutions and countries.

3. Challenges and Limitations

ATMPs offer the potential of a one-treatment cure. Both comparative effectiveness data and cost-effectiveness data vs. standard of care (often long-term symptom management) will be essential to show benefit with payers increasingly opposed to adding coverage for new technologies within small budgets. ATMPs are likely to meet problems at the extremes, such as when substantial clinical benefits (or cures) are offered at very high initial cost (Experts believe that new cell and gene therapies will cost an average of € 1 million or more) and benefits that accrue over a long-term period (see also figure 1).

Recognizing the large number of ATMPs under development, it is questioned whether current HTA models are suitable for the evaluation of these potentially curative therapies.

Additionally - although methodological guidelines developed, there is still much variation between HTA agencies.

As an overview, the following common challenges with ATMP commercialisation are summarized as such:

- High manufacturing, logistics and supply chain costs demand high reimbursed prices for commercial viability
- Variation in HTA methodologies across different EU markets as well as within individual countries across national, regional and local level assessments
- 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 centers 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)

- current HTA frameworks are not flexible enough to account for ATMP idiosyncracies 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 implemented due to high administrative burden, legal/accountancy constraints and also impact on manufacturer cashflow
- Lack of sufficient data collection infrastructure 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

4. Putative Solutions

Key goals in addressing commercialisation and challenges in early HTA tools for ATMPs

- Improve the methodological frameworks used in HTAs to capture the true value of ATMPs
- Support a single Joint Clinical Assessment at European Level (in line with the EU Commission Proposal on Health Technology Assessment Regulation, Jan 2018)
- 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

5. Challenges for RESTORE

In the table below, we outline a three-stage approach on how we could 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		Engaging 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	Engaging 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

As follows, suggested activities are described in detail in order to achieve the indicated goals:

1. Improve the methodological frameworks used in Health Technology Assessments (HTAs) to recognise the true value of ATMPs
    a. **Assess:** Conduct evidence reviews of ATMP HTA decisions across Major European Healthcare Markets (MEHM), and identify key limitations
    b. **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
        i. Identify methodological limitations and suggest strategies for improvement
    c. **Manage change:** Engage with HTA bodies and umbrella patient organisations to raise awareness and promote the implementation of methodological improvements
        i. Gather feedback from HTA bodies, umbrella patient organisations and industry stakeholders on the strategies for improvement

2. Manage payers' affordability concerns without restricting patient numbers
    a. **Assess:** Current payer management of budget impact concerns related to ATMPs through secondary and primary research with payer bodies in MEHMs
        i. Identify implicit/explicit budget impact thresholds

ii. 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

b. **Optimise:** Raise awareness around strategies to minimise affordability challenges through
   i. A series of workshops with European payer and industry stakeholders to explore the strategies identified above
   ii. Development of a white paper outlining potential solutions based on payer body feedback
c. **Manage change:** Engage with payer bodies in MEHMs to enable the implementation of these strategies

3. Reduce barriers to implementing performance-based reimbursement (PBR) schemes
   a. **Assess:** Barriers to implementing performance-based pricing (PBR) schemes from the perspective of payers and manufacturers
      i. How data collection infrastructure can be optimised to support longer term regulatory, reimbursement and product lifecycle data requirements across countries and therapy areas
         1. Analysis of national vs. cross-country infrastructure
            a. Assess the feasibility of upgrading existing registries to the functionality needed for PBR
            b. 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
            c. Assess the feasibility of a novel cross-therapy area and cross-country data collection infrastructure
      ii. Assess legal and accounting constraints and potential solutions
      iii. Assess third party finance solutions to overcome manufacturers concerns over cashflow challenges due to PBR
   b. **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
   c. **Manage change:** Engage with payers, umbrella patient organisations and industry representatives to support the implementation of a cross-country PBR pilot scheme

4. Increase the harmonisation between regulatory and HTA processes
   a. **Assess:** Liaise with HEOR and regulatory experts / centres of excellence to identify commonalities and differences between regulatory and HTA frameworks in MEHMs

b. Optimise: Identify and communicate opportunities to harmonise regulatory and HTA efforts through
    i. 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
    ii. Development of a white paper outlining potential solutions based on workshop feedback
c. Manage change: Support EMA and EUnetHTA in implementing pilot projects in priority area(s) identified

5. Develop tools to assist in valuation of ATMPs at the different stages of development
    a. 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
        i. Indication prioritisation (early/pre-clinical stage)
        ii. Identification of efficacy thresholds required for commercial viability (early clinical/pre-pivotal stage)
        iii. Development of cost-utility and budget impact analyses models that capture the true value of ATMPs (later stage, approaching launch)
    b. Optimise: Write white papers detailing preferred methodological tools for the different development stages

6. Develop tools to mitigate common challenges in evidence generation to support HTA
    a. 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.
        i. Long-term value claims are made extending well beyond the trial observation period
        ii. 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
        iii. Small trial size creates a challenge to statistical significance
        iv. Trials including surrogate rather than hard outcomes
        v. There are no (obvious) comparator treatments
        vi. There are no measures of outcome available (e.g. in certain very rare conditions, where these need to be developed)
    b. Optimise: Identify the preferred methodological approaches (from an HTA perspective) for tackling the evidence-generation/decision uncertainty challenges mapped out above through
        i. A series of workshops with EUnetHTA representatives to explore the methodological tools identified above
        ii. Define preferred methodological solutions to the challenges identified, and how these may differ across different MEHMs

c. **Manage change:** Develop methodological guidance documents on the most efficient evidence generation processes during clinical development (including clinical trial data, modelled data, other)

6. Summary

As described in the previous chapters, the processes of market authorisation of currently non-approved ATMPs may be confronted with recent HTA principles and practices. Deliberation of ways of dealing with increased doubts, for example, by developing outcome-based payment models or methodologies to recognise the true value of ATMPs, will be imperative. In particular, ATMPs may face a challenge in demonstrating value within current evaluative frameworks. In this document, we outline a three-stage approach on how the RESTORE consortium could 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. The proposed ways by RESTORE for optimization may be helpful in order to catalyze the dialogue around HTA for ATMPs. By transforming these recommendations into reality, the occasion exists to improve the HTA methods used for the assessment of ATMPs that would enable healthcare systems to manage some of the uncertainties and bring ATMPs closer to the market.

Section2. D4.4 Strategy paper on Health Economics & Reimbursement

1. Deliverables Description

Health economics and reimbursement for ATMPs rely on the effective HTA methodologies as discussed in section 1: D3.3. Therefore we will focus here on summarising issues most pertinent to the development of innovative payment mechanisms which will thereby allow rapid European ATMP adoption. In particular, we will emphasise the approaches necessary to ensure safe patient access to ATMPs, which ultimately is the unifying goal of RESTORE

2. State of the Art

Need for new reimbursement and business models

All relevant health institutions are increasingly accepting that new models for pricing and reimbursement may be needed to support adoption of Advanced Therapies. These efforts go hand in hand with reducing the cost of goods via disruptive approaches such as automation and non-viral methods for gene delivery, that are among the core principles of RESTORE. Indeed, several multi-stakeholder efforts are currently exploring new reimbursement models that enable payers to make their payments over time and/or enable payment tied to the therapy performance. The most common reimbursement models discussed in this context are annuity and pay-for-performance models (Cook F, Slocomb T, Werner M. Moving from chronic therapies to cures – creating a pathway to enable new payment models. 2017. www.alliance.org). These stakeholders include, but are not limited to, the The National Institute for Health and Care Excellence (NICE), Biotechnology Innovation Organization (BIO), the New Drug Development Paradigms (NEWDIGS) initiative at MIT, the Institute for Clinical and Economic Review (ICER), the American Society of Gene and Cell Therapy (ASGCT), and the Margolis Center for Health Policy at Duke University.

Critical to the success of Advanced Therapies and their adoption into the European market is the operational and business models necessary for such an approach to be commercially viable. RESTORE has a specific and dedicated focus to examining the potential commercialization strategies that can be employed to ensure that point-of-care availability of ATMPs is not just clinically viable but also commercially. In this regards, clinical hubs may be an interesting solution to some of the challenges e.g. the need for highly specialized treatment with the suitable infrastructure to collect real-world evidence , which in turn, will support any reimbursement model being used.

Pricing and Reimbursement Issues in Europe:

With the increase in the number of Chimeric Antigen Receptor (CAR) T cell therapies approved for patients with chemo-refractory or relapsed hematologic malignancies, for which only limited treatment options were available in the past, the issue of pricing and reimbursement has become more relevant than ever. The current price of CAR T cell therapies in the EU exceeds 320,000 euros, particularly when adding costs of hospitalization and treatment of side effects. Single-payer health care systems, which are predominant in the EU, are significantly

challenged by these prices. In spite of all these challenges, many patients pin their only hope on these novel therapies, which are being expanded to other malignancies, including solid cancers.
As such, heavy debate is ongoing with the focus on reducing costs and introducing suitable reimbursement models that can be accepted by statutory health insurance systems to prevent the uneven distribution of availability and affordability of these therapies.

3. Challenges and Limitations

Pricing strategies for ATMPs are mainly based on manufacturing costs, market size, and cost-utility analyses that consider the valuations of potential long-term benefits. As a result, such therapies are estimated in the high price range, considering the high costs associated with their manufacturing and the small market size, especially for orphan products.

1) Most of these products lack sufficient evidence on comparative clinical effectiveness due to the absence of a standard of care comparators in life-threatening and orphan diseases. This, in turn, may discourage healthcare payers from negotiating reimbursement strategies with developers.
2) As mentioned earlier, the HTA methodologies necessary to achieve a reimbursement agreement vary widely across different European member states, adding more complexity. For instance, the Swedish HTA is based on cost-effectiveness, human value, and solidarity, while in Germany, HTA assessment relies solely on cost-effectiveness analysis.
3) Due to the high upfront cost of developing cell and gene therapies, upfront payments has shown to be unfavorable for most payers

4. Putative Solutions

As a start, early engagement of scientists, clinicians, patient advocates and key opinion leaders should be considered so that ATMPs can have a chance for a possible market adoption process. This is one of the main principles of RESTORE. Other specific potential solutions include:

- Launching new initiatives to build Real World Evidence (RWE) infrastructure and disease registries at the pan-European level to collect more evidence on the safety and efficacy of these novel products
- Developers should be keen on demonstrating reasonable cost-effectiveness for their products at market launch by relying on reliable clinical endpoints and proper sample sizes in clinical trials.
- Coordinating ATMP clinical assessment at the EU level, while harmonizing HTA, pricing and reimbursement strategies to capture the actual value and potential long-term benefits and risks
- Facilitating cross-border treatment with ATMPs
- Issues such as uncertainty of coverage should be addressed to motivate healthcare providers to consider new cell and gene therapies that could improve patient care.
- Supporting the adoption of innovative pricing and payment models for ATMPs to ensure continued patient access to innovative therapies while preserving the sustainability of health systems in the EU e.g. support wider application of conditional reimbursement schemes

- Continue to streamline the manufacturing process of ATMPs and introduce new technologies that can reduce cost-of-goods.
- Addressing some of the financial sustainability challenges of health systems and developers in the different EU Member States.

5. Challenges for RESTORE

Building upon the 6 goals listed in Section 1:D3.3

1. Reduce barriers to implementing performance-based reimbursement (PBR) schemes

2. Optimize healthcare system infrastructure to support longer term regulatory, reimbursement and product lifecycle data requirements across countries and therapy areas

a. Assess the feasibility of establishing equipped clinical hubs for treatment of patients with ATMP

b. 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

c. Assess the feasibility of a novel cross-therapy area and cross-country data collection infrastructure

3. Assess third party finance solutions to overcome manufacturers concerns over cashflow challenges due to PBR

4. 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

5. Engage with payers, umbrella patient organisations and industry representatives to support the implementation of a cross-country PBR pilot scheme

6. Summary

As the development of Advanced Therapies becomes more streamlined and better clinical and manufacturing frameworks are developed, prices are expected to be reduced so reimbursement agencies and healthcare systems can afford these novel treatments. Until this is achieved, new reimbursement models need to be introduced to enable health insurance coverage and reduce out-of-pocket payments. Similarly, a dialogue should continue among all relevant stakeholders to harmonize models of clinical data collection and HTA. Eventually, this will not only help to reduce the cost burden on patients, their families, health insurance and tax payers but also decrease the economic burden associated with lack of curative treatments for chronic and debilitating diseases, for which ATMPs can become a viable therapeutic option.