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REAL-WORLD EVIDENCE ACROSS THE LIFECYCLE OF CELL AND GENE THERAPIES

FACILITATING PATIENT ACCESS

A Position Paper prepared by the EUCOPE Cell and Gene Therapy Working Group

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EXECUTIVE SUMMARY

Real-world evidence (RWE) is an important part of the policy landscape that will facilitate the future of Advanced Therapy Medicinal Products (ATMPs) in the EU. Action is needed by all stakeholders, including industry, to ensure the appropriate uptake of RWE can take place, ideally before the number of approved therapies grows. RWE plays a role both in facilitating Marketing Authorisations, as well as in post-Authorisation settings, addressing the inherent data uncertainties associated with ATMPs and supporting innovative payment and risk-sharing solutions. It is in the post-authorisation context where more barriers to the use of RWE exist, but major opportunities lay. As the EU revises the General Pharmaceutical Legislation, establishes the EU HTA procedures, and debates the European Health Data Space proposal, it is the opportune moment to update the EU landscape to embrace RWE in the context of ATMPs, building a future-proofed system. Policy solutions are needed at both EU and national level that promote the uptake of RWE across the ATMP life-cycle to help encourage access and embrace this wave of transformative innovation.

This paper consists of the following sections:

1. INTRODUCTION

The past 20 years have seen the gradual launch of advanced therapy medicinal products (ATMPs), in the European Union (EU), presenting patients with treatment options where, in some cases, no previous treatments were available[1]. This pace in innovation is not expected to slow down, with the number of new ATMPs available in the EU expected to continue growing over the course of this decade. The regulatory and pricing and reimbursement (P&R) experiences of the first ATMPs have illustrated some of the inherent challenges these therapies face, namely data uncertainties linked to the clinical trial data submitted at Marketing Authorisation and agreement on novel payment and risk-sharing models to optimise access pathways. Real-world evidence (RWE) has shown itself to offer a promising solution to many of these key challenges ATMPs face.

To ensure that patients benefit from these transformative therapies as soon as possible, establishing an appropriate RWE framework is key. The procedures that facilitate the assessment, access to and clinical uptake of ATMPs should be in place before a critical mass of ATMPs are on the market to avoid creating access barriers.

This paper explores the role and acceptability of RWE across the lifecycle of ATMPs, and its role in regulatory and market access pathways across the EU. As this paper will outline, RWE is particularly important in the context of ATMPs due to the challenges with traditional data generation approaches such as randomised control trials. It builds on the ongoing discussions that are taking place in a range of different contexts, including the European Medicines Agency (EMA) and alliances of which EUCOPE is a member, notably RWE4Decisions and TRANSFORM. This paper aims to bring together the discussions taking place in different fora to support ongoing legislative reforms and identify policy solutions.

The EU is currently undergoing a significant review of its pharmaceutical framework (General Pharmaceutical Legislation Review: Regulation No 726/2004 and Directive EC 2001/83/EC) and the Orphan Medicinal Products Regulation (Regulation 141/2000), while also expanding on the EU's role in coordinating health with the establishment of the European Health Data Space and defining the methodologies and procedures for the EU HTA procedure. This represents an opportune moment for the EU to reflect on and implement the needed RWE framework and ensure it is appropriate for the coming decades.

Definitions

[1] Ilieva, K., Borissov, B., & Toumi, M. (2020, January 1). Gene therapy randomised clinical trials in Europe – a review paper of methodology and design. *Journal of Market Access & Health Policy, 8*(1), 1847808. https://doi.org/10.1080/20016689.2020.1847808

While often grouped together, ATMPs cover a large range of different technologies. Even within the narrower classification of gene therapies, there are different technological approaches that employ a variety of modes of action in order to replace a faulty or missing gene[2]. More variables are introduced when considered the characteristics of the diseases that ATMPs aim to treat. A shared feature of ATMPs, is that they are potentially transformative and often require only one administration. For the purpose of this paper, ATMPs will refer exclusively to cell and gene therapies.

In this paper we define RWE as: *information derived from analysis of routinely collected Real-World Data (RWD)* where RWD means *routinely collected patient-level data relating to their health status and/or the delivery of health care from a variety of sources other than Randomised Control Trials (RCT)*[3]. As industry, hospitals and academic partners continue to run clinical trials for ATMPs, we expect to see a growing use of RWE, and of RWE combined with more traditional RCT designs.

2. CHALLENGES TO THE WIDER ADOPTION OF RWE BEYOND THE EU'S REGULATORY ENVIRONMENT

There are several factors that limit the use, implementation, and further roll-out of RWE beyond the immediate regulatory considerations in the General Pharmaceutical Legislation (GPL). The EMA has demonstrated an openness to the use of RWE[4]. It is essential that the GPL is updated so that it does not act as a barrier to the acceptability and uptake of RWE, but that its use is appropriately codified.

Challenges to the wider adoption of RWE include:

1. divergent requirements between key stakeholders, namely regulators, HTA bodies, and payers;
2. long-term adherence to data collection and the longevity of data registries;
3. a fragmented European data system.

Divergent requirements between key stakeholders

Regulators, HTA bodies and payers each have their own perspectives and responsibilities in the context of assessing novel therapies. As such, they often have different data requirements or interpret existing data

[2] International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (2020). Cell and Gene Therapies Toolkit. https://www.ifpma.org/wp-content/uploads/2020/09/IFPMA-IAPO-CELL-GENE-THERAPIES-TOOLKIT.pdf
[3] Cave, A., Kurz, X., & Arlett, P. (2019, April 10). Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. *Clinical Pharmacology & Therapeutics, 106*(1), 36–39. https://doi.org/10.1002/cpt.1426
[4] Flynn, R., Plueschke, K., Quinten, C., Strassmann, V., Duijnhoven, R. G., Gordillo-Marañon, M., Rueckbeil, M., Cohet, C., & Kurz, X. (2021, November 13). Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence? *Clinical Pharmacology & Therapeutics, 111*(1), 90–97. https://doi.org/10.1002/cpt.2461

differently. ATMP developers need to consider the different data requirements from the national HTA bodies and payers in 27 Member States.

These different data requirements and standards make it difficult to develop appropriate clinical trial protocols that incorporate RWE. Undertaking clinical trials is already a complex, time-intensive and expensive process. Having to undertake additional clinical trials that account for all the requirements across all Member States would significantly delay the launch of transformative therapies. Conducting additional clinical trials can be especially punitive for small and mid-sized companies.

The second complicating factor is that RWE might not be accepted by HTA bodies and payers. Uncertainty around the data quality and evidentiary requirements among these stakeholders adds a layer of uncertainty for ATMP developers. A core challenge is that authorities are asked to make an assessment on a therapy that might have life-long benefit, without a complementary data package. Thus, extrapolation would be required that goes beyond their normal timelines. A decision must be made while uncertainties exist about the effectiveness of the treatment[5].

Long-term adherence to data collection and the longevity of data registries

For post-authorisation RWE generation to be impactful, information must be collected consistently, and over a long time period.

Ensuring the longevity of data collection, often through data registries serves many purposes: providing pharmacovigilance data, generating a natural history data set, and acting as the basis on which novel payment and risk-sharing models can be built. However, ensuring the longevity of a disease registry that can remain active and complete for 10 -15 years is a challenge. Data might be lost, the collection of data can decrease, patients may opt-out of the programmes, or the responsible party may stop being active, e.g. due to a lack of funding. Ensuring that these challenges are overcome will be essential to facilitating and streamlining the successful uptake of ATMPs.

Beyond the storage of data, there are barriers to the appropriate collection of data. For a registry to be of value to ATMPs, it is important that consistent and appropriate data is collected. This responsibility often falls on physicians, representing an additional burden on their already limited time and resources[6]. Ensuring that the process of data collection is streamlined and simplified as much as possible for healthcare professionals is an important consideration for the longevity of RWE programmes moving forward. Digital health solutions, including patient reported data is one approach that could be explored.

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[5] *Generating Real-World Evidence in Outcomes-Based Managed Entry Agreements: Two Fictitious Case Studies.* (2021, June). Documents – RWE4Decisions. Retrieved September 7, 2022, from https://rwe4decisions.com/documents/.

[6] Khuran, M., & Kumar, A. (2018). Best Practices for Real World Evidence (RWE) Collection for Disruptive Technologies Like Cell and Gene Therapies. Https://Tools.Ispor.Org/Research_pdfs/60/Pdffiles/PHP187.Pdf.

Fragmented European data space

While ATMPs are centrally authorised, there are inconsistent data collection and augmentation methodologies[7] in data sets, both within disease areas as well as between Member States. As methods of data collection, health systems and patient populations can vary between Member States, interpretation of the collected data also differ between Member States, making it challenging to compare data collected across Member States. This is particularly challenging for rare diseases or diseases with a small target population where individuals are widely and unequally spread across the EU. The absence of a shared methodology for the collection of data, results in differences in what data is collected, both in a patient population but also between Member States. While a flexible approach is needed to ensure that data fits the needs of the various therapeutic solutions and is not overly cumbersome for healthcare professionals to collect, generating a host of different data sets is in and of itself a challenge, highlighting an area for increased EU coordination or guidance on data collection.

Additionally, the lack of harmonization in the implementation and interpretation of the General Data Protection Regulation (GDPR) requirements raises concerns about the sharing of data across borders or from different sources. This is particularly relevant for rare disease patients, due to the small number of individuals and risk of identifying patients despite anonymization.

3. WHY RWE MATTERS FOR ATMPS

The clinical data package and trial design are where ATMP Marketing Authorisation Applications (MAAs) often face objections[8]. RWE can play a key role in addressing and overcoming the different data uncertainties associated with the development and authorisation of ATMPs. It achieves this by contextualising clinical trial data and long-term efficacy and safety data to help manage risks and address concerns of different stakeholders, namely regulators, HTA bodies, and payers.

Clinical trials for Marketing Authorisation

Traditional therapies, such as small molecules or biologics, are more often tested and approved under randomised controlled trials (RCTs), commonly referred to as “the gold standard”. However, due to the nature of ATMPs, RCTs are often not feasible, practically possible[9] or ethical and face major logistical

[7] Strategies used in cases where there is limited data and additional data points are added by creating variations of existing data points in the existing data sets.

[8] Iglesias-Lopez, C., Agustí, A., Vallano, A., & Obach, M. (2021, December). Current landscape of clinical development and approval of advanced therapies. *Molecular Therapy - Methods & Clinical Development, 23*, 606–618. https://doi.org/10.1016/j.omtm.2021.11.003

[9] Iglesias-Lopez, C., Agustí, A., Vallano, A., & Obach, M. (2021, December). Current landscape of clinical development and approval of advanced therapies. *Molecular Therapy - Methods & Clinical Development, 23*, 606–618. https://doi.org/10.1016/j.omtm.2021.11.003

hurdles. Some of the key challenges[10] that ATMP developers can face when attempting RCTs include:

1. **Small and dispersed patient populations**: In many cases, ATMPs target rare indications, which by the very nature of the disease means that there is only a small patient population, which is often not located in a single geographic area. This can inhibit patient recruitment and the undertaking of large clinical trials.
2. **Patient populations need chronic dosing**: Patient populations with an established standard of care or approved therapy may require chronic treatment. Especially in cases of serious or debilitating conditions, stopping a treatment regime in favour of a placebo can have major and long-term implications.
3. **Lack of direct comparators for clinical and economic evaluation**: Many ATMPs are developed for indications that have few or no therapeutic alternatives or established clinical pathways.[11] Therefore, no direct comparators exist against which to test the ATMP and establish benchmarks.
4. **Limited specialized treatment centres to administer investigational products**: Due to the underpinning technology or preliminary interventions to prepare a patient to receive an ATMP, the products can often only be administered at specialized centres or centres of excellence, and may require specially trained healthcare professionals. These limitations can significantly restrict the size and scope of the clinical trials that can be conducted.

In some circumstances, the use of **RCTs can present ethical dilemmas**. Many of the diseases for which ATMPs are currently available are **rare or life-threatening**. The EMA recognises the existence of ethical challenges, stating that for ATMPs, there may be **circumstances where it would be unethical to use a placebo as a comparator**[12]**.** For instance, the delivery of some ATMPs may include invasive surgical procedures. Considering the fact that the target condition might be fatal and many have a genetic component requiring treatment at childhood, it raises ethical questions about the use of a RCT[13].

Given these limitations, the use of more appropriate methods for evidence generation, that incorporate RWE in single-arm clinical trials and natural history trial designs allow developers to demonstrate the impact and effectiveness of their therapies.

In this context, **the use of surrogate endpoints in the clinical trial design is also especially important**. It is unfeasible to have clinical trials that follow patients for their entire life, or extended periods of time. The

[10] These challenges do not apply to all ATMPs, and may not be unique to ATMPs alone.
[11] Ilieva, K., Borissov, B., & Toumi, M. (2020, January 1). Gene therapy randomised clinical trials in Europe – a review paper of methodology and design. *Journal of Market Access & Health Policy, 8*(1), 1847808. https://doi.org/10.1080/20016689.2020.1847808
[12] European Medicines Agency (EMA) (2019) DRAFT Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf
[13] de Melo-Martín, I., Sondhi, D., & Crystal, R. G. (2011, September). When Ethics Constrains Clinical Research: Trial Design of Control Arms in "Greater Than Minimal Risk" Pediatric Trials. *Human Gene Therapy, 22*(9), 1121–1127. https://doi.org/10.1089/hum.2010.230

use of RWE and surrogate endpoints constructed based on RWE, allow developers, regulators, and others to make more correct assumptions about the therapies and can reduce uncertainties in decision-making.

The EMA has already gathered importance experience with the use of RWE when it comes to assessing the quality, efficacy and safety of novel therapies[14]. Data presented at the October 2021 Committee for Advanced Therapies (CAT) Interested Parties meeting showed that all recent ATMP MAAs included some form of RWE to support single-arm trial data. However, regulators are at times limited by the barriers set out in the legislative framework. Therefore, the revision of the GPL should ensure that existing assessment frameworks allow for the more regular use of RWE and alternative evidence generation strategies when evaluating ATMPs. A stronger recognition and use of RWE is especially important where evidence is limited, e.g. rare diseases, and should be considered an effective complementary approach in addressing and resolving uncertainties that cannot be answered by traditional clinical trials.

The UK's National Institute for Health and Care Excellence (NICE) recently published their RWE framework, a living document that will evolve and provides support - rather than concrete rules - to developers looking to conduct RWE based clinical trials[15]. RWE should remain a tool to support the review of ATMPs, rather than a burden that could delay assessment, approval or access. A similar set of principles could be explored by the EMA and in the context of the Big Data Steering Group, allowing for robust trials, while maintaining an important degree of flexibility, reflective of the varying nature of ATMPs. These principles would complement specific guidance where the latter is deemed necessary, for example EMA's Guideline on registry-based studies[16], (under development) EMA reflection paper on single-arm trials[17], or ICH E10 Guideline on Choice of Control Group in Clinical Trials, including external controls[18]. France's HAS[19] and Germany's IQWiG[20] each have their own guidance on generating data based on RWE.

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[14] Arlett, P., Kjær, J., Broich, K., & Cooke, E. (2021, November 19). Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. *Clinical Pharmacology & Therapeutics, 111*(1), 21–23. https://doi.org/10.1002/cpt

[15] National Institute for Health and Care Excellence (NICE) (2022, June 23). NICE real-world evidence framework. http://www.nice.org.uk/corporate/ecd9/chapter/overview

[16] European Medicines Agency (EMA) (2021) Guideline on registry-based studies. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf

[17] European Medicines Agency (EMA) (2021). Committee for Medicinal Products for Human Use (CHMP): Work Plan 2022. https://www.ema.europa.eu/en/documents/work-programme/chmp-work-plan-2022_en.pdf

[18] European Medicines Agency (EMEA) (2001) Note for Guidance on Choice of Control Group in Clinical Trials. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf

[19] Medical, Economic and Public Health Evaluation Division (DEMESP) (2021). Real-world studies for the assessment of medicinal products and medical devices. *French National Authority for Health (HAS)*. https://www.has-sante.fr/upload/docs/application/pdf/2021-06/real-world_studies_for_the_assessment_of_medicinal_products_and_medical_devices.pdf

[20] Institute for Quality and Efficiency in Health Care (IQWiG) (2020). Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social

The development of a robust RWE framework, including in a post-authorisation setting, can support future clinical trials. RWE can help to contextualize clinical trial results, especially where natural history and single arm trials are necessary. The use of Bayesian Methods (whereby data from prior studies, such as previous clinical trials or disease registries, can be used in the ongoing trial to control for the reduced number of patients involved in a clinical trial) should be explored and encouraged as a mean to strengthen the robustness of RWE data.

RWE in Post-Marketing Authorisation context

The more significant challenge is with the uptake of RWE after Marketing Authorisation has been granted. HTA bodies and payers need to assess the clinical value and benefit of the treatment to make price decisions. However, due to the inherent data uncertainty linked to long-term efficacy, cost-benefit and pricing decisions must be made without the data that HTA bodies and payers would traditionally want. There is a need to balance the needs of HTA bodies and payers with what is practically feasible for developers to allow for the quickest possible access for patients. The appropriate and pre-agreed use of RWE can be used to address long-term data uncertainties and support novel payment and risk-sharing solutions.

By means of registries, stakeholders can measure and track the disease progression and impact of ATMP treatments on the patients, ensuring the collection of data in addition to that which was generated during the clinical phase. This data can be used to inform pricing and risk sharing agreements, support future clinical trials, and continue to monitor patient safety.

Addressing long-term data uncertainty

ATMPs routinely receive Marketing Authorisation despite some data uncertainties. This is a pragmatic approach as there is no viable solution for quantifying the long-term benefit (and risks) of the treatment. An unrealistic option would be conducting clinical trials that follow patients for the full duration of their life[21], something which would significantly delay access for patients not part of the study. To complement the studies already undertaken and further address the concerns of payer and HTA bodies, RWE can be employed to collect additional data on the efficacy of the treatment post-approval. Appropriate risk-sharing and payment models can be built around this approach to ensure patients access.

For these systems to be successful, they must be discussed and negotiated at an early stage of the therapies development, and stakeholders need to maintain an open dialogue. During the clinical stage, developers should engage with regulators, HTA bodies and payers at the right time and in appropriate

Code Book V. (No. A19-43). https://www.iqwig.de/download/a19-43_routine-practice-data-for-the-benefit-assessment-of-drugs_rapid-report_v1-0.pdf

[21] Conducting clinical trials that last the duration of a patient's lifetime face several key challenges that make them unviable and financially unsustainable, among them: the added expense associated with conducting the trials for such an extended period of time, the introduction of alternative variables in measuring the patients state, and the limitations of IP rights only lasting 20 years.

configurations. This will allow for clinical trials to be designed to collect the type of data each stakeholder needs in order to assess the treatment. It also serves as an important opportunity for industry to outline what is realistic and feasible in terms of data expectations. These discussions are especially important for small and mid-sized companies that may not conduct the clinical trials in-house. If developers are informed at the end of the process that different or new data is needed, they will need to incur additional costs and delay the launch of the therapy.

There is already established precedent in using RWE to validate the efficacy of a healthcare intervention in a post-Marketing Muthorisation and illustrate its effectiveness in a real-world setting. In the case of Hepatitis B vaccines, after their safety was established and made available for patients, the booster schedule was adapted based on real-world data to reflect the longevity of protection the vaccines offer.

ATMP payment and risk-sharing solutions

RWE can address the concerns associated with the price of the therapies and the lack of guaranteed long-term patient benefit, a bar that is higher than for other therapies. By agreeing to a joint RWE programme, developers and payers can implement innovative payment and risk-sharing models. Among these are models where payments are linked to pre-agreed health milestones, tracked through registries and RWE collection. Such an approach ensures that payers pay for clear patient outcomes rather than the therapy in itself. In addition, by having the cost of the therapy spread over several milestones, it reduces the perceived risk and upfront cost associated with the ATMP. These solutions directly address concerns associated about the outcomes and duration of effect for ATMPs[22].

An additional challenge to using RWE in ATMP pricing decisions is the fact that the same RWE can be interpreted differently by regulators, HTA bodes and payers. In some cases, different standards or types of data might be requested, which can place significant burdens on patients from which data is collected, physicians that most often collect the data, and industry which is often tasked with gathering the data, in order to collect the data in a practical and viable manner. Ensuring early and frequent dialogue between developers and different stakeholders to identify and align on viable evidence generation strategies would be an important development to improve access and support pricing decisions. In the future, based on such early engagement, RWE could be used to support more dynamic pricing strategies and decisions.

[22] EUCOPE (2021). Advanced Therapies Medical Products: New Payment and Funding Approaches. https://www.eucope.org/wp-content/uploads/2022/03/eucope-ipm-paper-2021.pdf

The experience from CAR-T cell therapies 5 demonstrates an interest in outcome-based reimbursements in Europe. Following their Marketing Authorisation approval by the European Commission in August 2018, Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel) managed to successfully obtain national reimbursement in Spain under a scheme including partial payment at the time of infusion, followed by a subsequent payment depending on each individual patient outcome. For a country not widely known for fast patient access, this model enabled a much swifter process for patients.

[23]

4. POLICY RECOMMENDATIONS

RWE can play a role throughout the life-cycle of an ATMP in order to expedite and improve access to these transformative therapies. Action will be needed by all stakeholders in the healthcare environment in order to maximise the possible benefit of RWE. In an effort to proactively contribute to the debate, EUCOPE proposes the following actions to support the use of RWE, spanning the life-cycle of ATMPs, addressing the challenges outlined in this paper. A number of these recommendations apply equally to both ATMPs and other therapies. EUCOPE supports the use of RWE in a broad context, while its use in the case of ATMPs exemplifies its potential impact.

1. Revise the General Pharmaceutical Legislation to **allow for the more regular use and acceptance of RWE and alternative evidence generation strategies**. The EMA's approval processes should accommodate use of RWE, alternative evidence generation pathways and adaptive clinical trial designs as an acceptable form of evidence for Marketing Authorisation Applications for ATMPs;

2. **Call for an updated and living framework document** including recommendations and methodologies for the use of RWE for regulatory purposes, including how RWE can be used to demonstrate safety and efficacy in the short and long-term, to be developed with input from stakeholders, including patients, clinicians and industry, and building on existing work, such as that of RWE4Decisions. In creating the framework and relevant principles and guidance, EMA should strive for international harmonisation, leveraging in particular the ICH forum;

3. Recommend the **creation of a multi-stakeholder EU learning network on RWE** to generate RWE that meets the needs of patients and healthcare systems;

4. **Remove obstacles to cross-border flow of health and personal data in the EU**. The European Health Data Space (EHDS) should lead to the adoption of EU-level data collection standards, data interoperability and harmonised exchange infrastructures. In addition, the EHDS should enable the establishment of efficient EU-wide disease registries that reduce barriers to the collection of RWE,

[23] APM Health Europe, 63646, 10 July 2019

duplication of efforts between Member States and grow common knowledge around diseases and treatments.

5. **Welcome the ambition behind the Data Analysis and Real World Interrogation Network (DARWIN EU)** project. To ensure the best possible use of DARWIN, all stakeholders, including developers should have access to the database, its analytical tools and be able to contribute with data from their clinical trials. There should be transparency about the design, objectives and results of RWE studies conducted through DARWIN EU, and about how they contribute to regulatory decisions.

6. **Call for clarity and harmonization regarding the application of GDPR provisions** to address the fragmented landscape caused by different Member State interpretations and remove barriers to the secondary use of electronic health data.

7. **Establish a framework for earlier and more frequent dialogue** between developers, regulators, HTA bodies, and payers in both formal and informal contexts to discuss evidence generation plans and acknowledge RWE as a justifiable evidence source. Stakeholders should be included when and where appropriate, in order to ensure that there is agreement and alignment on the data package early in the development process. This should not result in the creation of unrealistic expectations for the use of RWE in a Marketing Authorization context that would restrict and block access;

8. Call for the **Joint Clinical Assessments methodologies to reflect the specificities of innovative technologies such as ATMPs**, and accept evidence generated outside of the RCT design, including observational studies, single-arm trials and use of RWE;

9. Call for **Joint Scientific Consultations to be offered to all developers** under the EU HTA Procedure;

10. **Support investment** to establish the necessary IT infrastructure, human resources, data exchange formats, and methodologies to allow for the appropriate and long-term collection of RWE for use in both authorization and post-authorisation contexts.