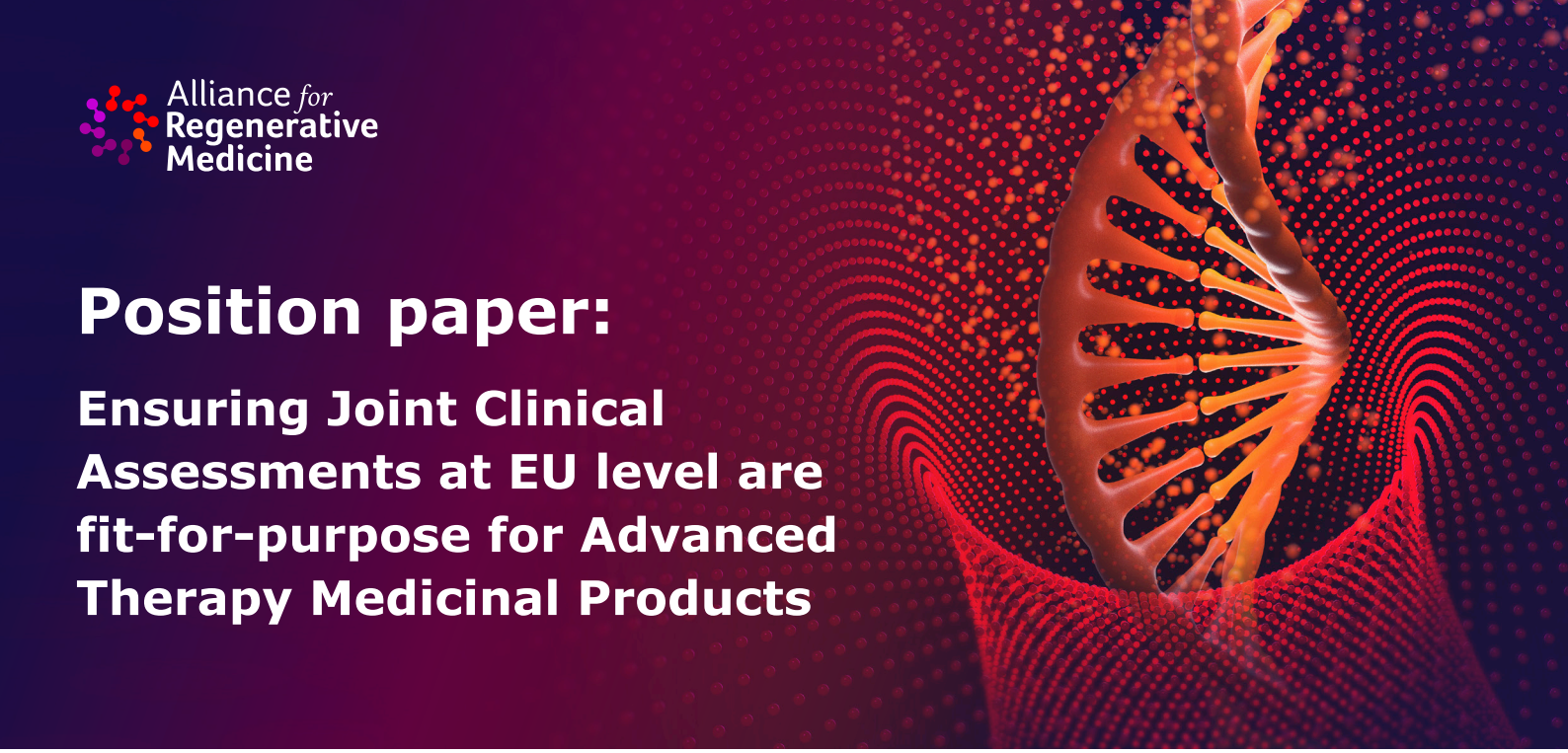
Alliance for Regenerative Medicine

Position paper:

Ensuring Joint Clinical Assessments at EU level are fit-for-purpose for Advanced Therapy Medicinal Products



Executive Summary

Following the entry into force of the EU HTA Regulation, Advanced Therapy Medicinal Products (ATMPs) will undergo EU Joint Clinical Assessment (JCA) starting from 2025. Due to their unique and transformative nature, ATMPs require fit-for-purpose methodologies that are different from the review processes designed for traditional pharmaceuticals. If the EU HTA process does not modernize its approach, the reviews will fail to capture the clinical value of ATMPs and jeopardize patient access to transformative therapies in the coming years. Such an outcome would call into question the value of the JCA process.

The unique characteristics of ATMPs

ATMPs in the EU are defined as medicines for human use that are based on genes, tissues, or cells. ATMPs differ significantly from conventional medicines in a range of areas, including the patient populations they serve, the diseases they treat, and how they are developed. ATMPs aim to address the root cause of disease, rather than the symptoms, and as such are potentially lifechanging for patients suffering from debilitating or life-threatening conditions, including rare and ultra-rare diseases.

Following the entry into force of the EU HTA Regulation, ATMPs will undergo JCA starting from 2025. The Alliance for Regenerative Medicine (ARM) is concerned that current JCA methods proposed by EUnetHTA21, which will input into the final methodology decided by the HTA Coordination Group, are unable to capture the full added clinical benefit of ATMPs.

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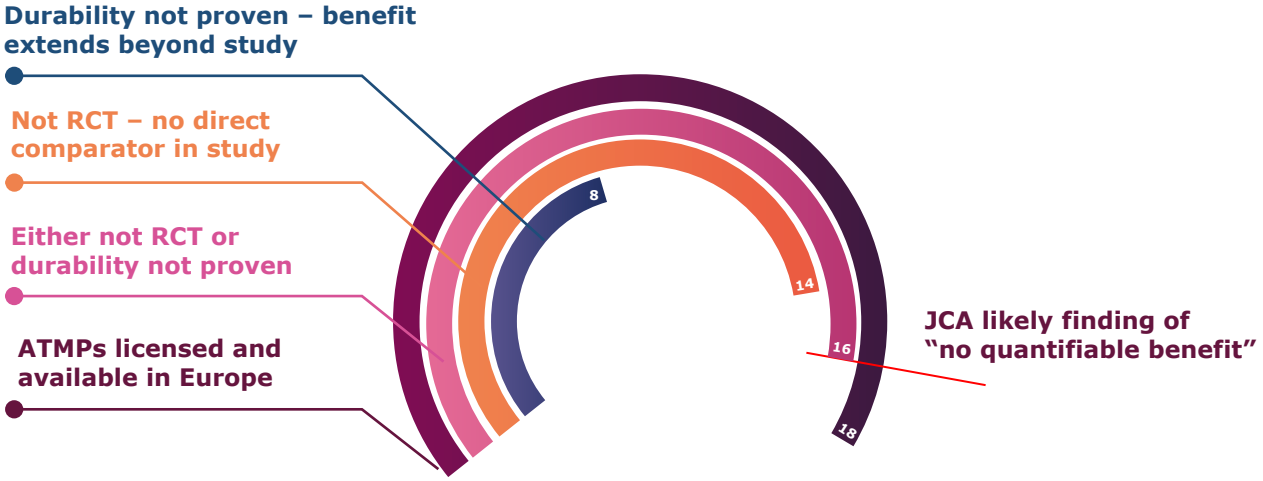
Traditional HTA assessments pose particular challenges for ATMPs

Because ATMPs are developed primarily for rare diseases and conditions without viable treatment alternatives, these treatments usually receive regulatory authorization with smaller datasets than traditional drugs. Applying a standard HTA methodology to these datasets would unnecessarily foreclose patient access to these treatments. Moreover, unlike traditional therapeutics, ATMPs promise long-term – and potentially lifetime – benefits, often with a single dose. As a result, pre-registration trials cannot reasonably be long enough to cover the full period of time a patient can benefit from treatment.

These aspects of ATMPs create some uncertainties in the assessments of their clinical added value at launch. In addition, due to their transformational nature and associated cost, the evidence presented is subjected to more intense scrutiny by HTA bodies. Due to the inherent differences in how ATMPs are developed and used, it is crucial that HTA methods are adapted so that the enormous promise ATMPs offer to patients is not sacrificed because of evidentiary uncertainties at the time of launch. Indeed, an analysis by ARM found that nearly 90% of the ATMPs licensed and used in Europe would have been rejected if a standard HTA methodology (including a demand for RCTs and proof of durability at launch) had been applied. These include all ATMPs for blood cancers and rare diseases, including multiple myeloma, mantle cell lymphoma, spinal muscular atrophy, hemophilia (A and B) and metachromatic leukodystrophy.

Emerging JCA methodology would have likely rejected nearly 90% of ATMPs currently licensed and marketed in Europe



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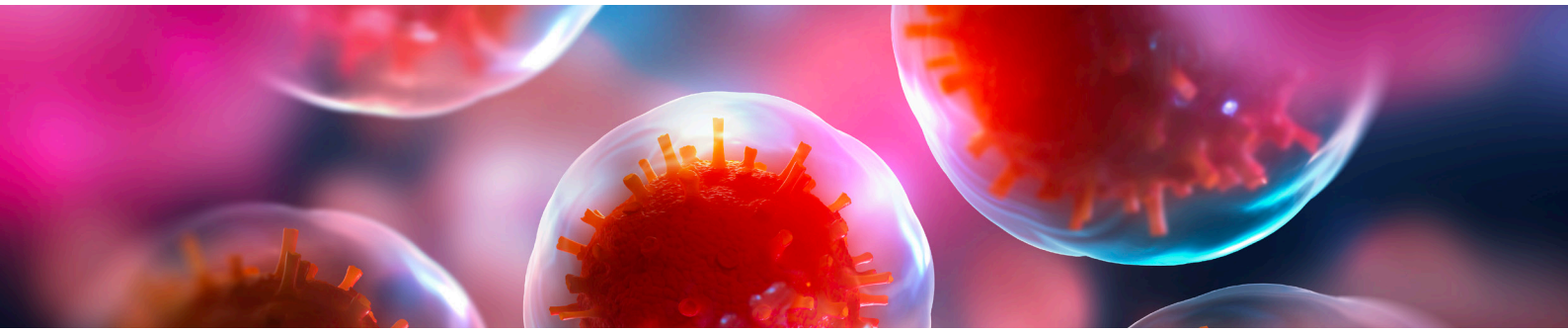
HTA bodies are beginning to recognize and adapt to these challenges

A number of EU countries and the UK have attempted to find alternative solutions to address the above challenges to ensure patients can access these potentially lifechanging therapies, while also ensuring that public funds are spent wisely. This shows an appetite to reconsider more 'traditional' HTA methods, particularly in light of the growing pipeline of ATMP therapies.



For instance, the Swedish HTA agency TLV has accepted data from a limited patient population for rare diseases[1], whilst the UK's HTA agency NICE has allowed for the extrapolation of clinical benefit beyond the small trial population.[2] Over in Germany, the G-BA has accepted methods for indirect treatment comparisons (instead of via RCTs), an issue which is particularly challenging for ATMP developers in areas where placebo control would not be ethical.[3] As a final example, the French HTA body HAS has, for certain products, requested to collect data on long-term outcomes through registries to resolve uncertainties about the long-term clinical benefit of an ATMP.[4]

There are therefore many encouraging examples where HTA bodies recognize that a different approach needs to be taken to evaluate ATMPs. This is not only happening on a case-by-case basis, but also increasingly via the development of novel HTA methods. In Europe, France's HAS is an example of an HTA body who is leading in this regard, having published in 2021 guidance on best practices for real-world evidence generation,[5] an important resource that could be leveraged to develop an EU-level real-world evidence generation plan. Just recently, HAS published in February 2023 its new HTA methodology which is more accepting of evidence uncertainties in the case of promising therapies.[6]

EU Joint Clinical Assessments should reflect advances made by countries to adapt HTA methods to ATMPs

ARM applauds the steps taken by a number of HTA bodies to adapt their methodologies to the proper assessment of ATMPs, which will only continue to increase in number. However, ARM remains concerned that the proposed guidelines developed by EUnetHTA21 are not fit-for-purpose. Specifically, ATMP development programs cannot mimic the trial size, treatment comparison, and confirmation of lifetime durability that traditional methodologies would demand.

If the draft guidelines are adopted with the current, traditional approach by the HTA Coordination Group, ATMPs undergoing JCAs will receive inconclusive recommendations. Inconclusive JCA results for ATMPs would mean that each country would have to replicate the assessment to arrive to a conclusion, and thus go against the objectives of the European Commission to accelerate patient access to innovative therapies via a unified assessment.

ARM calls upon key decisionmakers such as the HTA Coordination Group, the EU institutions, and Health Ministries to consider the below five recommendations to ensure that the final JCA methodology is adapted to recognize the particularities of ATMPs and their transformative potential for patients in Europe.

[1]TLV 2019. Health economic assessment of Luxturna in the treatment of visual impairment caused by hereditary eye disease.

[2]NICE 2021. Onasemnogene abeparvovec for treating spinal muscular atrophy.

[3]G-BA 2020b. Nutzenbewertungsverfahren zum Wirkstoff Tisagenlecleucel (Neubewertung nach Fristablauf: Akute lymphatische B-Zell-Leukämie).

[4]HAS 2020a. Choices in Methods for Economic Evaluation.

[5]HAS 2021b. Methodological guide - Real-life studies for the evaluation of medicinal products and medical devices.

[6]HAS 2023. Doctrine de la commission de la transparence (CT). Accessible here: https://www.has-sante.fr/upload/docs/application/pdf/2021-03/doctrine_ct.pdf

[7]A detailed outline of the recommendations can be found further below.

Key takeaways: ARM Recommendations

As part of the JCA process, the JCA Coordination Group should identify sources of uncertainty and ways to address these beyond the pivotal trial.

EU-wide guidelines for RWE generation should be clear and address country-level dynamics and use in EU JCA.

The guidelines on direct and indirect comparisons should provide clear guidance on appropriate methods and relevant sources when the evidence of a new therapy comes from a single-arm study.

The future JCAs should take a pragmatic approach in relation to uncertainty with conditional assumptions to be adapted when new data has been generated.

There should be continued collaboration with ATMP developers from the time of Joint Scientific Consultations (JSC) to the end of the JCA process.

ARM Recommendations

ARM has identified the following recommendations to address existing JCA methodological gaps when assessing ATMPs:

01

As part of the JCA process, it will be critical for the JCA coordination group to identify sources of uncertainty and ways to address these beyond the pivotal trial

As observed in past national HTA appraisals, the dataset available for an ATMP at launch will not resolve all uncertainty about the treatment, given the difficulties in carrying out large and controlled studies, for example in rare diseases without viable treatment alternatives, and the limitations in demonstrating long-term benefit at the time of appraisal.

During the EU JCA procedure, the assessors should engage in a dialogue with the developer to agree on a set of key outstanding uncertainties, along with the potential data sources to resolve them (e.g., natural history datasets, other clinical trials, network meta-analysis and indirect treatment comparisons with single-arm clinical trials, etc.) and an EU-wide plan to generate RWE that would address the uncertainties identified.

In addition to providing guidance on relevant and preferred sources, the EU JCA should take a pragmatic approach in assessing relative effectiveness under conditions of uncertainty, providing clear information on what is known with a sufficient degree of certainty and on the outstanding evidence gaps. This type of approach is already carried out by NICE with committees having greater discretion over whether specific uncertainties may be accepted on a case-by-case basis to enable decision making and help prevent barriers to access.

02 EU-wide guidelines for RWE generation should be clear and address country-level dynamics and use in EU JCA

Interest in RWE collection and use to complement evidence from clinical studies is steadily growing. Legislation in Germany now gives G-BA the authority to require collecting RWE through registries and other HTA bodies like NICE and HAS have developed or are in the process of developing guidelines on approaches to using RWE.

Despite these initiatives, there is still a lack of harmonisation between countries regarding guidance on the most appropriate approach for collecting this evidence to use during an HTA appraisal. For this reason, the JCA coordination group should liaise with key stakeholders with experience in RWE to create clear guidelines on the most relevant approach in the context of a JCA.

03 The guidelines on direct and indirect comparisons should provide clear guidance on appropriate methods and relevant sources when the evidence of a new therapy comes from a single-arm study

While some HTA bodies in Europe accept the use of indirect treatment comparisons, there is a lack of harmonization across countries on preferred approaches and methodology, as well as their level of acceptance. With the EUneHTA21 ongoing consultations, there is an aim to harmonize the approaches to indirect comparisons across Europe.

However, the EUnetHTA draft deliverable that was used for consultation did not have clear proposed methods on the most appropriate approach for carrying out indirect comparisons when evidence comes from a single arm trial. In addition, the draft deliverable (D.4.3.2) refers to the results from statistical approaches that have been proposed for cases of non-randomised evidence (such as single arm studies) and from observational studies and registries as “controversial”.

As previously mentioned, given the rarity of ATMP target diseases, the high unmet need in these conditions, and the significant clinical effect of ATMPs, it is often not appropriate or ethical to set up controlled trials for these types of therapies. Therefore, ATMPs are frequently studied in single arm trials.

The new methodology should provide clear guidance on non-RCT frameworks, including the use of indirect treatment comparisons and preferred approaches for resolving uncertainties at launch. These approaches include methods for measuring uncertainty and evidence development plans for mitigating such uncertainties. There are examples and published methodological guidance on the use of different approaches for indirect comparisons that EUnetHTA21 could leverage for their recommendations.

There is one further hurdle to the comparator issue. Given that there is likely to be variation in the standard of care across different countries, it is expected there will be a challenge with the proposed scoping process as presented in the draft deliverable (D4.2). The process as currently planned will be based on a PICO survey with all Member States, which may lead to a large number of comparators being requested for one specific therapy. This issue, coupled with the current uncertainty regarding the most appropriate approach and sources for indirect treatment comparisons in the context of single-arm trials, creates a lack of efficiency and operational feasibility for health technology developers. Therefore, ARM has urged EUnetHTA21 as part of the Scoping consultation to take a pragmatic approach in discussion with relevant stakeholders.

04 The future JCAs should take a pragmatic approach in relation to uncertainty, with conditional assumptions to be updated when new data has been generated

Similar to recent changes in NICE methods that allow for greater flexibility in the assessment and management of uncertainty, ARM urges the JCA agencies to accept conditional assumptions when assessing long-term treatment effect. These assumptions should be updated over time through RWE and evidence collected via other methods (e.g., involvement of clinical experts, patient representatives, etc.) as ways to reduce this uncertainty.

05 There should be continued collaboration with ATMP developers from the time of Joint Scientific Consultations (JSC) to the end of the JCA process

Early scientific advice has been used by health technology developers and HTA bodies to identify areas of uncertainty and issues in clinical development plans to better design pivotal studies and identify areas of additional evidence needs. For ATMPs, these engagements have accelerated time-to-access, as was the case for voretigene neparvovec in England following early engagements with NICE.

Future JSC engagements should continue to be leveraged to identify areas of uncertainty related to the PICO parameters. ARM would like to encourage that these engagements start at the initial stage of continued cooperation between EU stakeholders and ATMP developers prior to the JCA, as part of a synchronised and collaborative process, so that any evidence uncertainties can be identified early and addressed using the most appropriate methodology.

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Nearly 90% of ATMPs available in Europe were licensed without an RCT or complete proof of long-term durability

Emerging JCA methods would reject these and similar future treatments

Would Not Find Quantifiable benefit*

May Find Quantifiable benefit

Key to treatment names: Black: CAR-T Blue: Gene Tx Green: Other Cell

Name	Indication	Direct comparator in study	Durability question satissfied at launch?*
Imlygic	Melanoma	GM-CSF	✓
Spherox (chondrosphere)	Articular Cartilage Lesion of the Femoral Condyle	Microfracture	✓
Luxturna	LCA (blindness)	Untreated	✗
Hemgenix	Hemophelia B (severe)	Factor IX replacement#	✗
Yescarta	2L LBCL	✗	✓
Breyanzi	2L LBCL (TRANSFORM)	✗	✓
Ebvallo	Post-Transplant Lymphoproliferative Disease	✗	✓
Roctavian	Hemophilia A	✗	✗
Holoclar	Limbal cell deficiency in cornea due to burns	✗	✗
Abecma	Relapsed refractory multiple myeloma	✗	✓
Strimvelis	Adenosine deaminase deficiency	✗	✗
Tecartus	Relapsed refractory mantle cell lymphoma	✗	✓
Carvykti	Relapsed refractory multiple myeloma	✗	✓
Kymriah	RR B-cell ALL	✗	✓
Zolgensma	SMA	✗	✗
Libmeldy	Metachromatic leukodystrophy (MLD)	✗	✗
Upstaza	AADC deficiency	✗	✗
Alofisel	Complex anal fistulas in adult Crohn's disease	✗	✓

- **Programs with either no comparator (not RCT) and/or with the durability of benefit exceeding the length of the trial would likely be assessed with 'no quantifiable benefit'**
- **Every gene therapy would be rejected based on lack of proven long-term durability**

+ Assumes 'no benefit' finding on either lack of randomization/comp[arator or absence of proven durability

* Reflects the assumption that durability of benefit is of primary interest with non-oncology gene therapies

The same patients were evaluated, first on Factor IX replacement (6 months) and then on Hemgenix (24 months)

Source: www.clinicaltrials.gov (as of March 1, 2023) and EMA website, EMA EPAR reports, Galen/Atlantica analysis


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