Proposed joint clinical assessment methodology would have rejected nearly 90% of the ATMPs currently authorized in the EU

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Without changes recognizing the unique characteristics of ATMPs, the EU's new Joint Clinical Assessment will fail to deliver the next generation of transformative therapies to rare disease patients, according to the Alliance for Regenerative Medicine, EveryLife Foundation for Rare Diseases, and Rare Diseases International.

Nearly 90% of the Advanced Therapy Medicinal Products (ATMPs) currently authorized in the EU – including all seven gene therapies for rare genetic diseases — would have been rejected under the baseline methodologies proposed for the EU joint clinical assessment (JCA) starting in 2025, the Alliance for Regenerative Medicine (ARM) said Tuesday.

ARM reviewed the 18 ATMPs with EU marketing authorization, including cell and gene therapies for serious, sometimes fatal genetic diseases and blood cancers. The methodologies proposed by the EUnetHTA-21 consortium for consideration by the HTA Coordination Group would have rejected 16 of those ATMPs because long-term durability could not be proved at launch, they were not studied in randomized control trials (RCTs), or both. This includes gene therapies for spinal muscular atrophy and metachromatic leukodystrophy, two rare and often fatal genetic diseases that affect 550-600 infants born in Europe each year and one in 100,000 live births, respectively.

"There is a clear risk that rare disease patients in the EU – many of whom face death or serious disability – will not benefit from the next generation of transformative cell and gene therapies under the JCA methodologies proposed by the EUnetHTA-21 consortium," said ARM CEO Tim Hunt. *"We urge the HTA Coordination Group to develop a modernized framework for the JCA rather than defaulting to conservative approaches that were built for yesterday's pharmaceuticals."*

EUnetHTA-21 proposed requiring evidence from RCTs because they are considered the 'gold standard' for traditional pharmaceuticals. Incremental benefit can be determined by comparing a randomly chosen cohort of patients receiving the treatment with a randomly chosen cohort receiving a placebo. But the methods developed for traditional pharmaceuticals are not suited for the arrival of ATMPs, which can deliver a profound, durable, and potentially curative impact in a single dose. Single-arm trials are often medically, scientifically, and ethically necessary in the case of ATMPs. Patient populations in rare diseases are small, the diseases targeted advance rapidly and leave small windows for treatment, and there are often no treatment alternatives.

It's also not feasible to use the length of clinical trials to determine the durability of ATMPs' treatment effect – clinical trials would need to last for decades and perhaps

lifetimes. However, there are ways to address evaluators' concerns about the durability and efficacy of ATMPs in the absence of RCTs.

Comparing single-arm results to a synthetic comparator from a robust disease registry can provide evidence of added benefit, while gathering real-world evidence (RWE) post-approval can provide evidence of durability not available at the time of approval.

"As life-altering and life-saving therapies are emerging, we must ensure that the approaches employed across our ecosystem reflect the urgency, unmet need, and complexity of our rare disease communities," said Annie Kennedy, Chief of Policy, Advocacy, and Patient Engagement at the EveryLife Foundation for Rare Diseases. *"We applaud ARM for leading an approach to the modernization of the JCA process, and the ongoing commitment to ensuring that all available evidence is utilized in evaluations of ATMPs. For it is only when approved therapies can be accessed by eligible patients that they have value."*

Some national HTA bodies – including the Haute Autorité de Santé (HAS) in France and the *Gemeinsamer Bundesausschuss* (G-BA) in Germany – have taken innovative approaches that can serve as instructive examples for the EU JCA, including an openness to the use of registries and using indirect treatment comparisons instead of RCTs. The EU JCA should reflect the most innovative thinking from Member State HTAs, rather than the most conservative approaches.

"On behalf of the global rare diseases community, which has the most to benefit from cell and gene therapies, we urge the EU JCA to take the most enlightened and patient-centred approach to the assessment of ATMPs," said Durhane Wong-Rieger, Chair of Rare Diseases International. *"We also call for the greater inclusion of patients throughout the process so that patients' views on the benefits of life-saving therapies are incorporated into the assessment."*

ARM proposes several recommendations to modernize the JCA process and to maintain robust evaluations of ATMPs:

- 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
- 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 updated 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 will provide guidance on the JCA process and methodologies as a member of the EU HTA Stakeholder Network, which had its first meeting on June 14.

"ARM is ready and eager to work with HTAs and other stakeholders to develop a JCA process that delivers ATMPs to patients while addressing the needs of healthcare systems," said Paolo Morgese, ARM's Head of Public Affairs, Europe, and representative to the HTA Stakeholder Network.

ARM is hosting a panel discussion — *"What impact will the new EU Joint Clinical Assessment have on the competitiveness of Europe in the ATMP sector?" – as part of an event co-hosted with ATMP Sweden in partnership with the Swedish Presidency of the EU Council, focused on the future of advanced therapies in Europe. European Competitiveness in Advanced Therapies: How Do We Fulfill the Potential for the Benefit of Patients?* will take place on the 27th of June from 14:00 – 17:00 CET at the Karolinska Institute, Aula Medica in Stockholm.
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About the Alliance for Regenerative Medicine
The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments.

As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.