Call to Action of Concerned Stakeholders on the Implementation of the EU HTA and Joint Clinical Assessment for ATMPs

JCA should not hamper access to transformative ATMPs

We, the signatories of this statement, are a **group of patients, clinicians, academic medical centers, and therapeutic developers and manufacturers** with a strong interest in the successful roll-out of the Joint Clinical Assessment (JCA).

With the adoption of the **Implementing Act on the JCA for medicinal products[1] and the HTA Coordination Group's Methodological and Practical Guidelines on direct and indirect comparison[2]**, the implementation of the JCA under the EU HTA Regulation[3] is entering a critical phase. We are concerned that European patients with few or no treatment alternatives will experience further delays and limitations in **access to potentially life-changing medicines**. This would defeat the purpose of the EU HTA and JCA which aspire to increase and accelerate patient access.

Our concern is that the adopted methodology for the JCA assessment deems the datasets on which most ATMPs are authorized as too unreliable and uncertain to be factored into the clinical assessment. By stating that single-arm or non-randomized evidence 'may well be … insufficient for estimation of the relative treatment effectiveness in the context of JCA'[4], the methodology appears to go against the specific mandate of the HTA Regulation, which leaves such a judgment to Member States, and limits the JCA to a 'description [not an evaluation] … of the degree of certainty of the relative effects.' While we agree that randomized controlled clinical trials (RCTs) are the gold standard and should be conducted whenever feasible; for many ATMPs - especially in the rare and ultra-rare disease space - RCTs are unfeasible for ethical and practical reasons.

With the world of medicine evolving very quickly, marked by innovative therapies such as ATMPs bringing promise to patients with the highest unmet needs, it is crucial that HTA methodologies evolve to embrace this scientific progress.

OUR CALL TO ACTION

Therefore, we urge the members of the HTA Coordination Group and its relevant subgroups, and JCA assessors to **recognize all types of available evidence including single-arm trials and RWE, and to use the JCA report to *describe,* rather than *judge,* any resulting uncertainty as to the treatments' benefits, as called for by the HTA Regulation**. A significant portion of outstanding uncertainty can be addressed at the national level during the appraisal phase and through the collection of RWE.

In so doing, the Coordination Group can lead the development of a fit-for-purpose JCA system that efficiently addresses the needs of healthcare systems, without obstructing patient access to transformative therapies.

The rationale supporting our call to action

We summarize below our views and recommendations on the importance of **a JCA process that reflects the spirit and the text of the EU HTA Regulation,** and that is **fit-for-purpose** for ATMPs to help make these transformative therapies available to patients across the EU.

The promise of ATMPs and the importance of the JCA for patients

1. ATMPs have delivered lifechanging outcomes for patients facing death or serious disability from conditions that often have no viable treatment options. By addressing the root cause of disease, rather than the symptoms, they hold the promise of long-lasting patient benefits following a single administration. ATMPs include cell-based therapies such as CAR-Ts for fast progressing cancers, and gene therapies for severe genetic and rare diseases such as spinal muscular atrophy (SMA), metachromatic leukodystrophy (MLD), and sickle cell disease.
2. The outcomes of Health Technology Assessment (HTA) processes are of crucial importance in determining whether patients gain access to these potentially life-saving treatments. In 2021 the EU HTA Regulation came into force, introducing a pan-European process assessing the relative clinical benefit of new treatments, the so-called JCA. The Regulation also specifies that value judgments as well as appraisals and reimbursement decisions remain within the remit of Member States.
3. The JCA has the potential to create a more efficient system across the EU by centralizing one element of HTA - the clinical assessment - traditionally performed on a country-by-country basis. It could significantly reduce the time and costs of bringing potentially curative therapies to patients in the EU.
4. The promise of the JCA will only be realized, however, if the assessment methodology is appropriate also for ATMPs. Indeed, without a fit-for-purpose approach, the JCA could even introduce a new barrier to patient access. The insistence on RCTs in the final JCA methodology guideline – even in cases where such trials are not feasible – would create such a barrier. The same goes for the challenging data and evidence requirements in the JCA Implementing Act.

Limitations of the type and amount of clinical data for ATMPs

5. ATMPs typically receive marketing authorisation based on clinical datasets that are smaller than those for more traditional therapies. For the vast majority of ATMPs, the European Marketing Authorisation is based on non-RCT studies.
6. Several factors render RCTs infeasible or unethical for such ATMPs, including:
    - **Small enrollable rare disease populations** often do not support multiple treatment arms
    - It is **unethical to deny treatment through placebo** in the case of severe progressive diseases and end-of-life patients that ATMPs treat
    - Often a **standard of care does not exist** or does not halt the progression of disease

- The **limited treatment window** for progressive degenerative diseases in children would be missed by assignment to placebo or standard of care
- The **complexity and burden of treatment** makes blinding or add-on trial designs infeasible and/or unethical

Moreover, the **large and transformational treatment effects** often observed in ATMP clinical trials further support the ability of single-arm trials to demonstrate efficacy.

Kymriah (2018), Zolgensma (2020), Libmeldy (2020), Ebvallo (2022) and Upstaza (2022) are some recent examples of ATMPs that received Marketing Authorisation and were reimbursed at Member State level based on single-arm trials.

Misalignment of ATMPs and JCA methodology defeats the purpose of JCA

7. We are concerned that the methodology for the JCA assessment, as adopted by the HTA Coordination Group on 8 March 2024, would deem the datasets on which ATMPs are authorized as too unreliable and uncertain to be factored into the clinical assessment. Indeed, the final '*Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons*' appears to call for disregarding evidence from single-arm trials, even though they may be the only evidence available for consideration.[5]
8. A 'blank' JCA report would cause Member States to reject promising medicines, or to start over in their assessment. At best, this would lead to inefficiency and delay while, at worst, it would prevent patient access to potentially lifesaving medicines.

The HTA Regulation calls for JCA tailored to ATMPs

9. The HTA Regulation specifically anticipated this situation, calling for the HTA Coordination Group to develop appropriate methodologies for assessing ATMPs and to take into account the more limited datasets that may be available for these treatments at launch.[6] It explicitly calls for the consideration of observational trials, real-world evidence, and other sources of data beyond RCTs.[7]
10. Moreover, while the HTA regulation limits JCAs to a "description [not an evaluation] … of the degree of certainty of the relative effects,"[8] the Guideline states that it is "incumbent on the assessor *to judge* whether this evidence is *sufficient* for adequate estimation of the relative treatment effectiveness."[9] As it is a Member State's prerogative to determine acceptable levels of evidence uncertainty, it is not appropriate for JCA assessors to make value judgements about whether evidence certainty is 'sufficient' to show a treatment's relative effectiveness.

Scientifically rigorous solutions are available for ATMP clinical assessment

11. The differences in the development and use of ATMPs from those of other medicines does not mean that a rigorous JCA is not possible. Scientifically robust methodologies exist that allow HTA to accommodate the type of clinical evidence generated for ATMPs. Real-world data, including data from well-designed patient registries, retrospective and prospective observational studies, can and should be used to provide context and comparison for single-arm trials on questions such as natural history of disease. These tools can be augmented, where available, by control arm data from prior RCTs.

SIGNATORIES

1. Active Citizenship Network (ACN)
2. Alejandro Da Silva Foundation (Spain)
3. Alliance for Regenerative Medicine (ARM)
4. Canadian Organization for Rare Disorders (CORD)
5. Cancer Patients Europe (CPE)
6. CCRM Nordic
7. Community Health Association (Romania)
8. Cystic Fibrosis Europe (CF Europe)
9. Dravet Syndrome Foundation (Spain)
10. European Association for Haemophilia and Allied Disorders (EAHAD)
11. European Association of Urology (EAU)
12. European Brain Council (EBC)
13. European Hematology Association (EHA)
14. European Leukodystrophy Association (ELA International)
15. European Liver Patient Association (ELPA)
16. European Multiple Sclerosis Platform (EMSP)
17. European Society for Blood and Marrow Transplantation (EBMT)
18. European Society for Paediatric Oncology (SIOPE)
19. European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (E.S.PKU)
20. European Society of Gene & Cell Therapy (ESGCT)
21. EveryLife Foundation for Rare Diseases
22. Fondazione Telethon
23. Genéthon
24. Gynecological Cancerpatients (Finland)
25. International Patient Organisation for Primary Immunodeficiencies (IPOPI)
26. International Society for Cell and Gene Therapy (ISCT)
27. Italian Federation for Rare Diseases (UNIAMO)
28. Opie Jones Foundation
29. Pancreatic Cancer Europe (PCE)
30. Partners for Patients (PFP) NGO
31. SMA Europe
32. Thalassaemia International Federation (TIF)
33. World Federation of Hemophilia (WFH)

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[1] European Commission, Commission Implementing Regulation (EU) 2024/1381 of 23 May 2024 laying down, pursuant to Regulation (EU) 2021/2282 on health technology assessment, procedural rules for the interaction during, exchange of information on, and participation in, the preparation and update of joint clinical assessments of medicinal products for human use at Union level, as well as templates for those joint clinical assessment, Ref. Ares (2024)1703728 – 05/03/2024.

[2] EU HTA Coordination Group ("HTA CG"), Methodological & Practical Guidelines for Quantitative Evidence Synthesis: Direct and Indirect Comparisons ("Methodological Guideline"), adopted 8 March 2024.

[3] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU ("the EU HTA Regulation").

[4] EU HTA CG, Methodological Guideline, p. 33.

[5] "For some interventions single-arm or non-randomized evidence may be the only evidence available for consideration. However, it may well be necessary to deem that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA." EU HTA CG, Methodological Guideline, p. 33 (emphasis added).

[6] "Methodologies for performing joint clinical assessments and joint scientific consultations should be adapted to include specificities of new health technologies for which some data may not be readily available. This may be the case for… advanced therapy medicinal products." EU HTA Regulation, Recital 24 (emphasis added).

[7] EU HTA Regulation, Recital 35.

[8] EU HTA Regulation, art. 9(1).

[9] EU HTA CG, Methodological Guideline, p. 33 (emphasis added).