JOIN4ATMP feedback to the European Commission consultation on the EU Biotech Act

Fondazione Telethon is submitting the feedback on the EU Biotech Act on behalf of the EU-funded JOIN4ATMP Consortium. JOIN4ATMP bring together specialists, physicians and researchers from fourteen academic and not-for-profit partners based in Europe, with the aim to accelerate the development of Advanced Therapy Medicinal Products (ATMPs) and make them accessible across Europe.

ATMPs, and in particular gene therapies for rare genetic diseases, have been drivers of innovation and generated hubs of excellence in the EU. This innovation has often originated from academic centres and not-for-profit developers. Yet, while EU frameworks ensure safety and quality, the current regulatory environment remains complex and resource-intensive for academic and not-for-profit developers. Therefore, from our perspective, the measures included in the Biotech Act should address also criticalities specific to the ATMP field and build an ecosystem facilitating academic and not-for-profit development of biotechnology products, especially for rare diseases.

This Annex is submitted as an integral part to the responses to the Questionnaire.

Contents

1. ATMP clinical development regulatory framework

JOIN4ATMP acknowledge that the EU Clinical Trials Regulation (CTR) has introduced notable improvements toward the harmonisation and alignment across Member States (MSs) for the development of medicinal products. Yet, its interpretation and implementation continue to vary widely, undermining harmonization efforts. Indeed, there are still areas of misalignment and fragmentation within the EU, especially for biotechnology medicinal products and ATMPs, that hinder the development of innovative medicines and fail to generate a competitive ecosystem. Therefore, a fragmented and inconsistent regulatory landscape across MSs remains the main barrier also ATMP developers face to develop medicines and place them into the market.

In several EU MSs, complex and multi-tiered approval frameworks contribute to procedural delays and regulatory uncertainty. Ethics committees and national competent authorities frequently lack the specialized expertise required for the evaluation of ATMPs, resulting in prolonged or inconsistent assessments. Moreover, frequent amendments to national regulations and high turnover within regulatory bodies further compromise continuity and coherence in the regulatory process.

These disparities across jurisdictions create a fragmented system that slows trial approvals and complicates multinational collaboration. In the absence of a unified EU approach, this lack of coordination continues to discourage mostly smaller organizations and delay the availability of innovative therapies for patients.

Furthermore, ATMP developers operate within an ecosystem that lacks clearly defined and structured pathways from discovery to market authorization. Academic, not-for-profit institutions and small-scale sponsors often encounter significant obstacles in navigating the transition from early-stage research to late-stage development, largely due to limited regulatory expertise. The absence of harmonized frameworks for feasibility assessment, regulatory consultation, and clinical trial coordination contributes to inefficiencies, delays, and fragmented progress across the region.

Although certain national systems have established robust infrastructures, these often function in isolation. Cross-border collaboration remains limited, and the inconsistent implementation of Hospital Exemption and Compassionate Use provisions contributes to disparities in patient access and data collection. Furthermore, scientific advice is frequently fragmented or difficult to obtain, resulting in repeated protocol amendments, administrative inefficiencies, and increased operational costs.

In the absence of a coherent development roadmap that integrates regulatory, financial, and operational support mechanisms, many promising therapies face significant barriers to progressing

beyond early clinical stages. This structural gap not only impedes innovation but also diminishes EU's strategic position in the increasingly competitive global ATMP landscape.

We advocate the establishment of a proportionate and risk-based regulatory framework. This should include streamlined pathways for early clinical translation and harmonized certification guidance across MSs.

The JOIN4ATMP Consortium recommend improvements of the EU regulatory framework with an impact on the ATMP field as follows:

- ATMPs national trials: the level of expectation by the assessors on the contents of the Clinical Trial Applications (CTAs) may vary greatly across MSs depending on the engaged Health Authority (HA), on the national policy, and on the expertise of the assessor, irrespective of the phase of the trial and on the recommendations to adopt risk-based approaches. Competitiveness among MSs may stimulate the implementation of more efficient systems, such as expedited/dedicated procedure to attract developers, but the level of expectation for the degree of detail of the information contained in the CTA (especially with regard to the quality part – Investigational Medicinal Product Dossier-Quality [IMPD-Q]) should be harmonised within the EU providing specific guidelines to the HAs and assessors. Asking for market-level requirements for Phase I/II clinical trials, and especially for low-risk products (that is for which prior knowledge and data packages obtained using the same technologies already exist), can be detrimental to early-stage development of ATMPs and discourages iterative processes necessary for innovation.
- ATMPs multi-national clinical trials: we advocate for the implementation, in CTA Part I and II Assessments, of automatic mutual recognition of the Reference Member State (RMS) Request for Information (RFI) and conclusions by the Member States Concerned (MSCs) at least for innovative medicines and ATMPs. The ethical assessment of Part II documents should be centralised and demanded to the RMS of MSC appointed to evaluate Part II documents (master document to be implemented locally) on behalf of all participating MSCs.
- Additionally, once an RFI has been responded to and approved regarding a specific question, it should not be subject to a subsequent RFI, even if a different assessor is appointed for the new request. This principle is essential to ensure procedural consistency and to avoid unnecessary duplication of regulatory efforts. Risk-based approaches and agreement on post-approval commitments can be applied in place of longer assessments.
- Also, as the EU is acknowledging the achievement of solid knowledge on ATMPs, which is leading to the decommissioning of the Committee for Advance Therapies (CAT) for marketed products, the additional 50 days foreseen by the CTR to consult with ATMP

experts during CTA assessment seem unnecessary and should be removed. In case the RMS proposed by the applicant has no internal expertise available, another RMS with the expertise required readily available should be appointed. In general, more reliance on risk-based approach and for instance implementation of post-approval commitments should be used instead of longer timelines.

- Mutual recognition of also ATMP Genetically Modified Organism (GMO) authorisations should be imposed on MSs. This should be the result of a reform of the GMO legislation, introducing amendments in the ATMP Regulation to harmonise GMO assessment for ATMPs across MSs. The assessment should be included in the current CTA procedure under the CTR or conducted in parallel, centralising in one EU portal all CT-relevant regulatory procedures. The first step toward this would be to implement a dedicated section for ATMP GMO assessment to conduct clinical trials (deliberate release) in CTIS to be used by MSs where this assessment is required for their national processes.
- EU ATMP consortia and coordination platforms should be established to align policies, funding mechanisms, and operational standards. A continent-wide Real-World Evidence (RWE) network, based on federated data models, would allow MSs to securely share safety and outcome data while safeguarding patient privacy. Joint funding initiatives and shared access to GMP and testing infrastructure would ensure equitable participation in innovation, particularly for smaller countries.

Additionally, it must be considered that efficient execution of ATMP clinical trials requires harmonized operational standards, enhanced recruitment strategies, and the integration of modern digital tools. Current delays are often driven by fragmented data collection, administrative complexity, and inconsistent training of personnel. Therefore, considering personnel requirements, the following proposals should be considered:

- Invest in continuous professional development for clinical investigators and trial coordinators, focusing on ATMP-specific regulatory requirements, safety protocols, and data management practices.
- Broaden eligibility criteria and implement adaptive trial designs to improve patient recruitment and ensure greater inclusivity in ATMP clinical studies.

The European Health Data Space (EHDS) provides a promising framework, but its implementation must consider the needs of academic hospitals handling sensitive clinical and biobank data. In this respect, a continent-wide Real-World Evidence (RWE) network, based on federated data models, would allow MSs to securely share safety and outcome data while safeguarding patient privacy.

Additionally, developing interoperable digital platforms for patient recruitment and monitoring has the potential to significantly improve trial efficiency, particularly in rare and paediatric indications. Broad implementation of electronic consent (eConsent) and remote safety monitoring can reduce administrative burdens while improving patient accessibility and engagement. Therefore, the following recommendations are proposed:

- Establish centralized ethics committees and adopt standardized review templates to streamline ethical evaluations and reduce administrative variability.
- Develop interoperable national and regional ATMP networks that connect research hubs with EU-level expert platforms, enabling efficient resource sharing and data exchange.
- Integrate real-world evidence generation into both the execution and follow-up phases of clinical trials to enhance safety monitoring and accelerate post-trial learning and regulatory feedback.

2. Implementation of the HTA Regulation

The Joint Clinical Assessment (JCA) centralised procedure introduced by the HTA Regulation (HTR) is a pivotal step forward in the direction of faster pricing&reimbursement processes and easier access to the fragmented EU market, with the potential to reduce the uncertainties related to the return on the investments and derisk development of medicines in the EU. Yet, entities developing ATMPs, in particular for rare diseases, would benefit from schemes beyond joint HTA. Building on the joint procurement of medicinal products of common interest foreseen within the proposal of the Critical Medicine Act, the introduction of EU-level "innovation procurement" mechanisms to fund late-stage development of ATMPs before MA would be a significant incentive to invest in the biotechnology sector. Indeed, HTA JCA alone may jeopardise access to single MS markets, when in the case a non-conclusive outcome is issued.

Furthermore, the current HTA framework is opaque and overly rigid from the patient involvement perspective, which impact the business case of companies developing biotechnology products as ATMPs, particularly around conflicts of interest and feedback to nominators in the case of patients affected by rare or ultra-rare diseases. Transparency and communication are essential to build trust and ensure that patient input remains credible and valued, therefore, more clarity and structure is needed.

For instance, the modality of involvement of patients in the definition of PICOs remains unclear. What are the criteria for engaging with one patient association over the other? Is national representativeness considered? Are pan-European association preferred? Also, are subgroups of the disease taken into account? This is pivotal for developers who might have already engaged a local patient group or a specific disease subgroup, which guided the development of an ATMP in a precise direction. Alignment of patient engagement during development with patient involvement for HTA assessment is needed to guarantee a balanced JCA procedure and successful entry in the market.

In detail, the Biotech Act may introduce amendments to the HTR to address critical aspects of the process:

- Extend the timeline for the Applicant to indicate a patient expert (currently one week only) and commit to follow up on the patient expert candidates selection&involvement after indication by the Applicant
- Consider the conflict of interest only pertaining to the natural person and not to the patient association. Indeed, expert patients for ultra-rare diseases can be very few. It may be very difficult/not feasible to meet the parameters for conflict of interest set out in

the Regulation. Also considered that not only expertise in the disease but also fluency in English is needed.

- Ensure HTA bodies are strengthened with sufficient resources, HTA consultation offers the possibility of early dialogue with HTA bodies, which is highly encouraged. Yet, sufficient resources must be provided by member states to guarantee that this interaction is accessible to all interested developers. The current planning of two consultation per year underscores the potential high number of orphan drugs that should be prioritised for such dialogue. Also, it poses the risk for a developer to miss the application/miss the opportunity, having to undergo HTA assessment without consultation. The opportunity for this dialogue cannot follow a lottery-like dynamic and prioritisation rules must be put in place.
- Reinforce the validity of single-arm trials as clinical avenues to produce high quality data that can and must be used during HTA assessment. In particular, single-arm trials should be indicated as viable options to produce HTA-relevant data in the case of ATMPs, especially for rare diseases, where randomisation is not feasible or unethical. Please, consider for reference the paper Considerations driving the choice in clinical trial design of cell and gene therapy products: weighing convenience versus necessity by Abrams K. et al. (doi: 10.1016/j.jcyt.2025.06.001). The work outlined a framework to assess when deviation from a randomised clinical trial is necessary and should be acceptable, and on how alternative study designs such as a single-arm trial or unblinded RCT may be justified. Specifically: where the experimental treatment is expected to have high efficacy but the enrollable patient population is too small; where there is no effective standard of care and patients assigned to placebo would experience significant disease progression during the trial; where subjecting the control group to complex, burdensome and potentially risky protocols in the interest of blinding would impose unacceptable burden on patients.
- The impact of the HTA JCA outcome on cross-border access must be taken into account. Many ATMPs, especially those for rare and ultra-rare diseases, are often administered only in qualified specialised treatment centres. There can be a few treatment centres for specific diseases, as low as one unique European treatment centre, in few or in a single member state (MS). A negative, or even non-conclusional JCA outcome may be leveraged to restrict access by a MS lacking a treatment centre, that is, where the ATMP is not commercialised. Indeed, such MS could not greenlight pricing & reimbursement procedures, or not be available to other pricing negotiations activated on request, necessary for NHS-sustained cross-border access, on the basis that the ATMP did not demonstrate sufficient efficacy and safety. Currently (based on two approved ATMPs that were developed at SR-Tiget, Milan, the single EU centre

where these ATMPS are administered), 25% of eligible patients do not obtain permission by its MS to access the cross-border treatment, so it is very likely that a higher percentage of patients will not have access to these therapies within this framework. In the case of ATMPs, where the evidence for the JCA assessment is often generated by single-arm trials, those must be included in the guidelines as sources of viable and high-quality evidence to avoid the risk of getting a refusal to be considered in the assessment or of biasing the assessment toward a non-conclusional outcome. Another solution would be to include in the HTR, for ATMPs, especially those with orphan drug designations, that once received a positive JCA outcome, the product enters in the basket of care of all MSs automatically, becoming a right of the patients residing in all MSs; the MSs will have then to adopt the pricing negotiated by the MS where the treatment centre is. This could be further implemented as followed:

- framed as an innovative procurement scheme for specific product types, such as orphan drugs and innovative ATMPs;
- managed through a joint procurement as laid out in the Proposal for a Regulation on supply critical medicinal products (Critical Medicines Act)
- linked to the existence of a centralised fund dedicated to cross-border access and coverage of expenses in the case of ATMPs, especially for rare diseases.

3. Innovative avenues toward ATMP registration and novel licensing schemes

Notwithstanding the many improvements toward a unified market, the EU drug market does not exist while developers face 27 different national markets. This has a strong impact on the "speed of reaching the market" as the market is not reached at the time of Marketing Authorization but, in many countries, only months (or even years) later, when the price and reimbursement process is completed. This remains an unpredictable timeline, different from country to country, in spite of the ameliorations introduced by the HTR as commented in Section 2. This makes EU less attractive to investors as it adds another layer of uncertainty (both on timing and outcome of the negotiation) in the estimation of the Return on Investment (RoI). On the contrary, in the US the BLA approval potentially triggers immediate commercialization of the therapy.

Furthermore, with regard to registration of medicinal products and marketing licensing, the MHRA in the UK is acknowledging that conventional regulatory pathways designed for common diseases are challenged by rare diseases and in particular by ATMPs developed for rare genetic diseases. Therefore MHRA has very recently (2 November 2025) announced that it is setting up a new implementable regulatory model in 2026, whose impact must be carefully considered on the EU biotechnology ecosystem (https://www.gov.uk/government/publications/rare-therapies-and-uk-regulatory-considerations/rare-therapies-and-uk-regulatory-considerations). Indeed, MHRA committed to adopt a more flexible licensing approach in this area. Development of this new pathway is driven by the principle of enabling a risk-benefit assessment to be appropriate for the target disease and target patient population. This will cover non-clinical, clinical and manufacturing areas and will include: a guidance for the use of prior knowledge, clarity on terminology and expectations on Platform definitions, tiered and risk-based approaches to prepare stage-appropriate Applications.

In particular, among novel registration and licence structure, MHRA is introducing an Investigative Licensing Pathways where preliminary approvals may be granted based on appropriate, albeit limited, evidence such as mechanism hypothesis, with iterative reassessment throughout the process.

The EU must consider implementing equally flexible measures for rare diseases and ATMPs to safeguard the biotechnology ecosystem and avoid that developers massively shift clinical development and then seek early approval in the UK via this novel licensing route to fund further product development and evidence-generation to achieve full-registration of innovative therapies. We advocate for such measures as follows:

- Implement a novel MA for personalised ATMPs, specifically for rare, ultra-rare and N=1 diseases. Such registration avenue should adopt a risk-based approach to accept

incomplete but solid clinical evidence to grant an “exploratory” of “preliminary” marketing licence in the EU. This licence would increase speed, flexibility, competitiveness and patient’s access in the context of a rigorous regulatory framework that would bridge clinical trial with a full marketing authorization. This personalised ATMP licence would be monitored and assessed annually and subject to commitments and obligations until a satisfactory level of high-quality safety and efficacy data is achieved. This novel registration pathway may also rely on prior knowledge and data packages generated during the development of similar ATMPs that already obtained regulatory approval for at least an early clinical phase. This registration avenue would be of particular relevance for ATMPs at an early stage of clinical development, relying on the same platform technologies, based on the similar/same mechanism of action. In this view, additional personalised ATMP MAs would be granted cross-referencing a master personalised ATMP MA. This novel MA path would differ from MAA under exceptional circumstances as it is intended for an early, preliminary approval which does not preclude a full approval. Different from hospital exemption, it would allow to collect data in the context of a clinical trial and permit rapid patient’s access and reimbursement across Europe.

- Furthermore, JOIN4ATMP strongly support the introduction of Platform marketing authorisation registration in the Proposal for a Directive part of the general EU pharma reform (Section 3, Article 15), where the approved medicinal product (MP) can be tailored in its pre-defined variable component to meet the characteristics of patients. However, a platform approach should be promoted and implemented also during the early phases of clinical translation for ATMPs relying on the same technologies, whilst safeguarding patient safety and ensuring the most direct path to standalone individual MAs. We therefore recommend to:
    - Allow the submission of a matrix design of studies that can ensure the generation of robust and exhaustive “platform” data packages from very early development stages to avoid the necessity of repeating studies at a later stage, jeopardizing MA achievement.
    - Considered that there is little to no opportunity for platform approaches based on identical end-to-end process and controls without adaptation, allow the submission of manufacturing processes and CMC controls defining components in the process that can be identified as modules, constituting plug-and-play elements that could be cross-referenced across multiple programs with the importance placed on the inputs and outputs and an appropriately understood design space from modules rather than fixed parameters.
    - Data from both development stage and authorised ATMPs should be leveraged when defining platform modules. The programs collectively contribute generated

data to the consolidation or adaptation of the process/drug product design space within the modular platform framework.

- An a priori definition of the quantum of data to justify specific modules/components as a “platform” cannot be defined. Such definition would follow a case-by-case and risk evaluation-based process, also considering the intended use of the platform and clinical risk/benefit evaluation.
- The platform concept must safeguard the possibility to leverage data packages that constitute the transversal totality of data across sponsors to enable maximised efficiency to all associated development programs.

4. Funding and compliance costs

Funding and compliance costs remain two of the most significant and persistent barriers to the advancement of ATMP clinical trials. Academic and hospital-based sponsors often face challenges in sustaining research beyond early-phase studies, while critical infrastructure, such as GMP manufacturing facilities and digital trial systems, remains unevenly distributed across regions. Ensuring long-term sustainability will require predictable, multi-year investments that integrate both public and private sector commitments.

To address these challenges, we advocate:

- the establishment of a coordinated ATMP Clinical Trials Alliance at both national and EU levels could streamline feasibility assessments, contracting processes, and pharmacy support, thereby providing a unified operational backbone for all trial sponsors.
- The creation of dedicated innovation funds to support SMEs and academic institutions, complemented by a robust digital infrastructure for trial management, registries, and post-trial monitoring. In parallel, strengthening national and regional bioinformatics capacity will be essential to ensure EU can manage and analyse complex datasets in line with international standards.
- Finally, in the initial version of the New Fee regulation, the principles outlined as premises stated the necessity to provide fee reductions dedicate to SMEs also to non-profit and academic developers:

(20) In line with Union policies, it is appropriate to provide for reductions of the fees to support specific sectors and applicants or marketing authorisation holders, such as micro, small and medium-sized enterprises (SMEs). In addition to commercial entities, not-for-profit organisations and the academic sector can play an important role in the development of medicines. However, fees can present a significant obstacle for those entities that are not engaged in an economic activity. For that reason, they should equally benefit from fee reductions, provided that [...]".

> Nonetheless, non-profit and academic developers are not included in the fee reductions reserved to SMEs and listed in ANNEX V,1 to the New Fee regulation. This should be amended to fully comply with the principles laid out in the Premises to the regulation. Indeed, academic and not-for profit entities are developing ATMPs up to MAA filing facing the hurdle of paying fees reserved to big industries in the field. Therefore, fee reductions also for registration and post-marketing phases are relevant for academic and not-for profit entities, not limited to the pre-registration development phases such as fee reductions for Scientific Advice (ANNEX V,2.1).

The business case of ATMPs for rare and ultra-rare disease is particularly fragile and not attractive for capital investors. Possible solutions would be to create:

- Social impact investment funds to support not-for-profit development of ATMPs. Such funds, accepting a lower rate of return on their investments, could invest also in low rewarding therapies that are not attractive for typical Venture funds.
- A transferable voucher linked with marketing authorization that could allow to ensure developers and additional income on top of those generated by the commercialization of the drug. Such a voucher, modeled on the US priority review voucher, should be linked to a commitment by the developer to keep the product on the market for N years after marketing authorization. This incentivising measure would provide accelerated assessments (for CTA and/or MAA), and could be applied to specific product types, such as orphan drugs and innovative ATMPs that reach defined regulatory milestones (eg. OD obtaining MAA; ATMP obtaining ad hoc to be defined designations for innovativeness).
- Innovation procurement schemes in the drug market. Some EU Member States do already have early access schemes where the treatment is reimbursed by the healthcare system (e.g. Law 648 in Italy or ATU in France). However, those early access schemes are not designed as innovation procurement mechanisms to accelerate the development of therapies but, if well structured, they could serve also that purpose.