ATMPs Under EU HTAR: Structural Challenges and Mitigation Strategies for Rare Disease Development

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Executive Summary

The fundamental misalignment between Health Technology Assessment (HTA) requirements and the realities of rare disease Advanced Therapy Medicinal Products (ATMP) development manifests across multiple dimensions of clinical evidence generation [1].

Clinical trial design becomes particularly problematic when dealing with small, geographically dispersed patient populations that make traditional randomized controlled trials ethically questionable and practically unfeasible [2].

Endpoint selection and validation present additional hurdles, as rare diseases often lack established outcome measures that can demonstrate meaningful clinical benefit within the timeframes and sample sizes that HTAR assessments require [3]. The implementation of the ICH E9(R1) estimands framework, while scientifically rigorous, creates additional complexity when applied to heterogeneous rare disease populations where individual patient responses may vary dramatically and intercurrent events can significantly impact small study populations [4]. Furthermore, the requirement for long-term evidence generation to demonstrate sustained benefit becomes resource-intensive and methodologically challenging when following small cohorts over extended periods while maintaining statistical power and clinical relevance [5].

These structural challenges require innovative approaches that balance scientific rigor with pragmatic recognition of rare disease development constraints, requiring enhanced collaboration between regulators, HTA bodies, health technology developers, and patient communities to ensure that transformative ATMP treatments can reach patients with rare diseases while maintaining appropriate evidence standards for safety and efficacy assessment [6].

Introduction to ATMPs and EU HTAR Context

Advanced Therapy Medicinal Products (ATMPs) encompass a diverse range of innovative therapeutic approaches including gene therapies, somatic cell therapies, tissue-engineered products, and combined ATMPs that integrate medical devices with biological components [7, 8].

These cutting-edge treatments represent a paradigm shift in medicine by offering potentially curative interventions for previously untreatable conditions, particularly in the rare disease space where traditional pharmaceutical approaches have proven inadequate [9]. The EU Health Technology Assessment Regulation (EU HTAR), formally designated as Regulation (EU) 2021/2282, was implemented in January 2022 with full application beginning in January 2025 (oncology and ATMP scope), establishing a comprehensive framework for joint clinical assessments (JCAs) of medicinal products across European Union (EU) Member States [10]. This regulation aims to harmonize clinical assessment methodologies, reduce duplication of evaluation efforts between national HTA bodies, improve predictability for health technology developers, and ensure consistently high-quality, patient-relevant assessments across the European healthcare landscape.

The HTAR mandates robust comparative clinical evidence demonstrating meaningful clinical benefit, standardized methodological approaches that align with established scientific principles, and comprehensive assessment frameworks that evaluate new treatments against current standards of care [11].

The intersection of HTAR requirements with rare disease ATMP development creates unique challenges that stem from the fundamental characteristics of rare diseases and the innovative nature of advanced therapies [12].

Rare diseases (defined in the EU as affecting fewer than 5 in 10,000 people) have inherently small patient populations that limit traditional clinical development and statistical approaches. Many rare diseases have poorly characterized natural histories due to limited research, making it difficult to establish appropriate comparators and disease trajectories.

Real-world evidence (RWE) including natural history studies provides longitudinal insights into disease evolution and routine clinical management. They can be a support to investigate disease progression, clinical heterogeneity, outcome trajectories, and patient variability. They also support identification of clinically relevant populations, characterization of genotype–phenotype relationships, selection of inclusion/exclusion criteria, and validation of novel biomarkers.

These studies provide precise epidemiological data, enabling researchers and healthcare providers to understand patient numbers at national and local levels.

Clinical Trial Design: Challenges and Mitigation Strategies

Clinical Trial Design Challenges

The fundamental challenge confronting rare disease ATMP development under EU HTAR lies in the inherent contradiction between regulatory and HTA requirements for robust comparative evidence and the practical limitations imposed by small patient populations [2,13]. Rare disease patient populations are typically numbered in the hundreds or fewer globally, creating immediate constraints on traditional clinical trial designs that assume adequate sample sizes for statistical power calculations [14]. These limited populations become further restricted when applying standard inclusion and exclusion criteria, often reducing eligible patients to numbers that make meaningful statistical analysis extremely difficult [15]. Recruitment challenges are compounded by geographic dispersion, as rare disease patients are scattered across countries and continents, requiring complex international collaboration and creating logistical barriers for centralized ATMP administration [16].

The ethical considerations surrounding control group assignment in rare disease trials present particularly acute challenges when dealing with potentially life-saving ATMPs. Traditional randomized controlled trial designs, which HTAR strongly favours, become ethically problematic when withholding potentially curative treatment from patients with progressive, irreversible conditions where no effective alternatives exist [17]. The use of placebo controls raises serious ethical concerns in rare disease populations where patients may have exhausted all available treatment options. Crossover trial designs may compromise the ability to generate long-term comparative data essential for HTAR assessment, particularly when dealing with one-time interventions that produce permanent genetic and/or cellular changes.

The heterogeneity within rare disease populations creates additional complexity, as many rare diseases encompass multiple genetic subtypes, varying ages of onset, and diverse clinical presentations that may respond differently to ATMP interventions [18]. This phenotypic variability means that small trial populations may not adequately represent the full spectrum of disease manifestations, limiting the generalizability of trial results and challenging the population-level treatment effect estimates that HTAR assessments require [19]. Geographic dispersion creates practical challenges for ATMP clinical trials that require specialized administration procedures and expert clinical teams typically available only at major academic medical centres. The limitation of natural history data for rare

diseases creates fundamental challenges in establishing appropriate comparators for HTAR assessment [20].

Standard of care for rare diseases may be entirely palliative, non-existent, or highly variable between treatment centres, complicating the establishment of meaningful control groups [21]. Disease heterogeneity within rare disease categories often means that patients with the same diagnostic label may have vastly different clinical presentations and treatment responses, challenging the population-level treatment effect estimates that HTAR assessments require. Additionally, the one-time or infrequent administration characteristic of many ATMPs requires novel assessment frameworks that can capture both immediate and long-term effects while accounting for the irreversible nature of many genetic and cellular interventions

Clinical Trial Design Mitigation Strategies

Innovative adaptive trial designs offer promising approaches to address the constraints of rare disease ATMP development while maintaining scientific rigor [15, 22]. Seamless Phase 1/2/3 trial designs can significantly reduce the total number of patients required by eliminating traditional boundaries between development phases and allowing for continuous learning based on accumulating data. Response-adaptive randomization techniques can ethically address concerns about withholding effective treatment by dynamically adjusting randomization ratios to favour treatment arms showing superior efficacy. Bayesian trial designs can incorporate prior information from preclinical studies and natural history data to enhance statistical power and enable meaningful conclusions from smaller sample sizes [23].

Platform trial approaches and master protocols can maximize the utility of limited rare disease populations by enabling efficient evaluation of multiple treatments within a single infrastructure framework [24]. Umbrella trial designs can evaluate multiple treatments for a single rare disease, while basket trials can assess single treatments across multiple rare diseases that share common biological pathways.

The development and validation of external control strategies provide alternatives to traditional randomized control groups while maintaining the comparative evidence framework that HTAR requires [25]. In that setting, natural history studies can serve as robust historical, non-concurrent comparator arms for single-arm investigational trials. When randomized controlled trials are unethical or infeasible, externally controlled studies based on high-quality natural history data can enhance the interpretability of efficacy and safety findings (MHRA draft guideline and FDA draft Guidance). Leveraging historical cohorts allows for a more comprehensive

contextualization of treatment effects and supports regulatory evaluation in the absence of an internal control group. Furthermore, European data networks enabling analysis across multiple healthcare systems can increase sample sizes and improve statistical power [26].

Propensity score matching techniques can create comparable control populations from natural history cohorts or disease registries [27]. Synthetic control arm approaches use statistical modelling to create virtual control populations, enabling comparison without withholding potentially beneficial treatment [28].

International collaborative frameworks can address geographic dispersion challenges by creating coordinated global approaches that maximize patient access while maintaining regulatory standards [29]. Multi-regional clinical trials with harmonized protocols can pool patient populations across countries [30]. Patient engagement strategies throughout clinical development can improve trial design, enhance recruitment and retention, and ensure that study outcomes reflect patient priorities [31]. Decentralized trial approaches using telemedicine and home nursing visits can reduce patient burden while maintaining data quality [32]. In that setting, when integrated early into development planning, well-designed, protocol-driven RWE such as natural history studies can meaningfully accelerate development timelines, reduce uncertainty, strengthen regulatory submissions, and improve the likelihood of both approval and reimbursement.

Endpoint Relevance: Challenges and Mitigation Strategies

Endpoint Relevance Challenges

The selection and validation of appropriate endpoints for rare disease ATMP assessment under EU HTAR present fundamental challenges due to small patient populations [3].

Most rare diseases lack validated, disease-specific outcome measures that have undergone rigorous psychometric evaluation necessary for regulatory acceptance [33]. The absence of established outcome measures means that health technology developers must often rely on generic functional assessments or biomarkers of uncertain clinical relevance. This creates a circular problem where the lack of validated endpoints impedes clinical development, while small patient populations discourage the substantial investment required for comprehensive endpoint validation.

The ongoing debate between surrogate and clinical endpoints becomes particularly complex in rare disease ATMP development [34]. Biomarker-based surrogate endpoints may enable earlier assessment of treatment effects, but they often lack validation studies necessary to establish their

relationship to clinically meaningful outcomes [35]. Clinical endpoints that directly measure patient function or survival may be more meaningful but often require years of follow-up to demonstrate meaningful changes. Many ATMPs may have delayed onset of action, requiring extended observation periods to capture their full therapeutic potential [36].

Patient-reported outcomes (PROs) represent a critical component of rare disease assessment, as patients, carers and families are often the most sensitive observers of meaningful changes. However, few rare disease-specific PRO instruments exist, and those that do often lack comprehensive validation studies [37]. Cognitive and physical limitations associated with many rare diseases may impair patients' ability to complete self-assessment instruments, requiring proxy reporting that introduces additional measurement complexity. The regulatory acceptance of novel endpoints creates additional uncertainty for Health technology developers who must balance scientific innovation with regulatory conservatism. Digital biomarkers derived from wearable devices offer potential for more sensitive assessment but lack established regulatory qualification pathways [38].

Endpoint Relevance Mitigation Strategies

Biomarker qualification programs offer a systematic approach to developing and validating surrogate endpoints that can support rare disease ATMP development [39]. Collaborative qualification consortia that bring together multiple stakeholders can share the substantial costs required for comprehensive biomarker validation studies [40]. The establishment of clear context of use specifications helps define appropriate application of biomarkers within specific rare disease populations. The development of biorepositories that collect biological samples from rare disease patients enables retrospective validation studies [41].

Patient preference studies provide a systematic approach to the understanding of which outcomes are most meaningful to rare disease patients [42]. Preference elicitation studies using techniques such as discrete choice experiments can quantify patient preferences for different treatment outcomes [43]. Benefit-risk preference assessment can inform regulatory and HTA decision-making by providing quantitative evidence of patient willingness to accept risks in exchange for potential benefits.

Composite endpoint development offers an approach to creating more sensitive outcome measures that capture the multisystem nature of many rare diseases. Disease-specific composite endpoints combining multiple relevant domains can provide more sensitive detection of treatment effects than individual components alone. Regulatory science initiatives provide a framework for advancing methodological approaches to endpoint development that can benefit the entire rare disease community [44].

The integration of digital health technologies offers innovative approaches to endpoint development that can provide more sensitive, frequent, and patient-centred assessment [45]. Wearable devices can enable continuous monitoring of physical activity and physiological parameters in patients' natural environments. Smartphone-based applications can facilitate frequent assessment of cognitive function and patient-reported outcomes while reducing patient burden. Artificial intelligence-assisted analysis of complex movement patterns or speech characteristics can identify subtle changes not apparent through traditional clinical examination [46].

In that setting, natural history data are instrumental in the development and validation of biomarkers and in establishing endpoints that reflect disease progression and patient experience. This includes the identification of potential surrogate endpoints that may support accelerated development pathways. Such evidence is particularly critical in settings where traditional endpoints are impractical, insufficiently sensitive, or require prohibitively long follow-up periods.

Estimands Framework: Challenges and Mitigation Strategies

Estimands Framework Challenges

The implementation of the ICH E9(R1) estimands framework in rare disease ATMP development presents unique challenges stemming from small patient populations and heterogeneous disease characteristics [4]. Defining appropriate estimands requires clear specification of the population of interest, but rare diseases often encompass genetically and phenotypically diverse patient groups that may respond differently to treatment [47]. The variable of interest must reflect clinically meaningful outcomes, but rare diseases often lack validated outcome measures, creating uncertainty about which variables best capture treatment benefit. The handling of intercurrent events becomes particularly complex when each patient represents a substantial percentage of the total study population.

The challenge of handling intercurrent events in small/rare disease populations creates disproportionate impact on study interpretation. When a study includes only dozens of patients, the occurrence of intercurrent events such as treatment switching or rescue therapy can dramatically affect the ability to estimate treatment effects. Each patient who experiences an intercurrent event represents a substantial loss of statistical power and may introduce bias. Standard statistical approaches for handling intercurrent events may be underpowered when applied to very small sample sizes.

The tension between population-level and individual patient estimands becomes particularly pronounced in rare disease ATMP development, where treatments often demonstrate highly variable individual responses. EU

HTAR focuses on population-level treatment effects, but rare disease treatments frequently show transformative effects in some patients while providing little benefit to others.

Estimands Framework Mitigation Strategies

Flexible estimand strategies that acknowledge the unique characteristics of rare disease populations can provide a framework for meaningful treatment effect estimation while maintaining scientific rigor [48]. The specification of multiple estimands addressing different stakeholder perspectives can provide more comprehensive assessment of treatment effects. Sensitivity analyses exploring different approaches to handling intercurrent events can demonstrate the robustness of treatment effect estimates [49]. Early alignment with regulators on primary estimand selection can reduce development risk.

Bayesian statistical approaches offer particular advantages for rare disease populations by enabling incorporation of prior information and providing more flexible frameworks for small sample analysis [23, 50]. Informative priors based on disease biology or preclinical studies can enhance statistical power and enable meaningful conclusions from smaller sample sizes. Hierarchical models that borrow information across patient subgroups can improve estimation precision while accounting for heterogeneity [51]. Bayesian decision frameworks incorporating utility functions can provide more nuanced assessment of treatment benefit.

Multi-stakeholder alignment on estimands and analysis approaches is essential for ensuring that rare disease ATMP development programs generate evidence meeting all decision-makers' needs [52]. Early dialogue between health technology developers, regulators, and HTA bodies can identify areas of agreement on evidence requirements and areas of important differences that must be accommodated or acknowledged as challenging to accommodate. Patient input on meaningful treatment effects can inform estimand definition and ensure study outcomes reflect patient priorities [53]. The development of guidance specific to rare disease estimand implementation can provide clarity and consistency for health technology developers.

Long-term Evidence Requirements: Challenges and Mitigation Strategies

Long-term Evidence Requirements Challenges

The generation of long-term evidence for rare disease ATMPs presents a fundamental challenge stemming from small patient populations, resource constraints, and the evolving nature of healthcare systems over extended time periods [5]. Extended follow-up studies face the challenge of maintaining patient engagement and data quality over many years while dealing with natural attrition. When starting with small patient populations,

even modest rates of patient loss can substantially reduce statistical power and introduce bias. The resource intensity of long-term monitoring becomes particularly challenging for rare disease ATMPs, where commercial returns may not justify the substantial investment required.

The evolution of standard of care over time creates additional complexity for long-term evidence interpretation, as improvements in supportive care can affect the relevance of historical comparisons [54]. Patients who received ATMPs years earlier may have access to new supportive therapies not available at initial treatment, making it difficult to attribute long-term outcomes specifically to the ATMP intervention.

Real-world evidence generation faces particular challenges in rare disease populations where infrastructure for systematic data collection may be limited [55]. The lack of standardized data collection in clinical practice means that real-world outcomes may be captured inconsistently across different healthcare providers. Selection bias in treated populations becomes a significant concern when ATMPs are available only at specialized centers [56]. Other challenges include a lack of sufficiently granular data in RWE sources to accurately measure baseline confounders, difficulties in replicating trial inclusion and exclusion criteria, poor data quality, an undefined study baseline, and inherent differences between clinical trials and routine practice. These factors impact monitoring, supportive care, outcome measurement, and other critical aspects of data collection and analysis [56].

Long-term Evidence Requirements Mitigation Strategies

Conditional approval and Exceptional Circumstances pathways offer a framework for balancing timely patient access with long-term evidence generation by enabling market authorization based on preliminary evidence while requiring ongoing data collection [57]. The utilization of regulatory designations such as PRIME can provide enhanced regulatory support for long-term evidence generation planning [58]. Conditional marketing authorizations with comprehensive evidence generation plans can specify the type and scope of post-marketing studies required [59]. Outcomes-based managed entry agreements can create financial incentives for long-term evidence generation while sharing risk between health technology developers and healthcare systems [60].

Registry-based trials are particularly relevant for evidence generation in the post-launch phase of a treatment. Real-world data collection strategies leveraging existing healthcare infrastructure can provide cost-effective approaches to long-term evidence generation [61]. These trials can address remaining uncertainties identified during regulatory and health technology assessment (HTA) evaluations, providing valuable insights into long-term effectiveness and safety in real-world settings.

Post-authorisation surveillance optimization can enhance the efficiency of long-term monitoring while reducing burden on patients and healthcare systems [62]. Mandatory long-term follow-up registries with standardized data collection protocols can ensure systematic capture of safety and efficacy outcomes. Electronic health record integration can leverage existing healthcare data systems to capture real-world outcomes without requiring additional infrastructure [47]. Patient-driven reporting mechanisms can enable direct capture of patient-reported outcomes while reducing burden on healthcare providers.

International registry harmonization can address the global nature of rare disease populations while creating more robust evidence generation platforms [63]. The development of core outcome sets specifying essential measurements can improve data comparability and enable pooled analyses [64]. Managed entry agreements and innovative payment models can create financial incentives for long-term evidence generation while addressing uncertainty about treatment durability [65]. Outcomes-based reimbursement schemes tying payment to demonstrated long-term benefit can align financial incentives with evidence generation requirements [66].

Regulatory and Policy Recommendations

The complexity of rare disease ATMP development under EU HTAR necessitates enhanced dialogue and coordination between regulatory agencies and HTA bodies to ensure that evidence requirements are aligned, feasible, and focused on clinically meaningful outcomes [67]. Joint scientific advice procedures specifically designed for rare disease ATMPs should be established to provide coordinated guidance from both regulatory and HTA perspectives, reducing the risk of conflicting requirements. These parallel consultation processes should include meaningful patient involvement to ensure that evidence generation plans reflect patient priorities while meeting regulatory and HTA standards [68]. The alignment of evidence standards and methodological approaches between agencies can reduce development uncertainty and enable more predictable pathways to market access.

The development of rare disease-specific guidance addressing the unique challenges of ATMP development can provide clarity and consistency for Health Technology developers while encouraging methodological innovation [69]. ATMP-specific considerations should be integrated into existing rare disease guidance documents to address the particular challenges of gene therapies and cell therapies. Methodological guidelines for small population trials should provide practical advice on study design and statistical analysis that acknowledges rare disease development constraints while maintaining scientific rigor.

Conclusion and Future Outlook

The structural challenges facing ATMP development for rare diseases under EU HTAR represent a fundamental tension between the scientific rigor necessary for evidence-based healthcare decision-making and the practical constraints imposed by small patient populations, limited resources, and the unique characteristics of rare diseases. These challenges manifest across the entire clinical development continuum, from initial trial design through long-term evidence generation, requiring innovative approaches that balance methodological sophistication with pragmatic recognition of rare disease development realities. The successful implementation of mitigation strategies requires unprecedented collaboration between stakeholders, including Health Technology developers, regulators, HTA bodies, academic researchers, and patient communities, all working toward ensuring that patients with rare diseases can access transformative ATMP treatments while maintaining appropriate standards for safety and efficacy assessment.

The most promising mitigation strategies identified share common themes of flexibility, innovation, and collaboration. Adaptive trial designs, external control strategies, and Bayesian statistical approaches offer methodological solutions that can generate robust evidence from small patient populations while maintaining scientific validity. Digital health technologies and patient-centred outcome measures provide new tools for capturing meaningful treatment effects that reflect patient priorities. The estimands framework, when applied thoughtfully to rare disease contexts, can provide clarity and transparency in treatment effect estimation. Conditional approval pathways, managed entry agreements, and international registry harmonization create mechanisms for balancing timely patient access with ongoing evidence generation requirements.

Conflict of Interest: Sylvie Bozzi, Celine Fernandez and Marie-Pierre Petitjean are employees of Sanofi. Ian Keyzor and Christelle Pierrot are employees of Astellas.

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