JOINT CLINICAL ASSESSMENT FOR ADVANCED THERAPY MEDICINAL PRODUCTS

Learnings from National HTA Reviews and Methodological Recommendations

Alliance for Regenerative Medicine

Evidera | PPD

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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 in 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.

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 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

1. Introduction

- ATMPs in the European Union (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 aspects associated with their clinical development and manufacture. ATMPs are generally characterised by small clinical trial populations commonly due to targeting rare diseases, uncertainties associated with clinical trial design considerations, specialized manufacturing often for individual patients, and usually restricted administration due to only being allowed in authorised centres. They also have the potential for long-term clinical benefit, often with a single administration.
- In the EU, ATMPs will undergo Joint Clinical Assessment (JCA) from 2025. Hence the Alliance for Regenerative Medicine (ARM) has created this report to draw lessons learned from recent clinical assessments of ATMPs at the national level and identify viable methodological approaches to be adopted with the EU JCA.

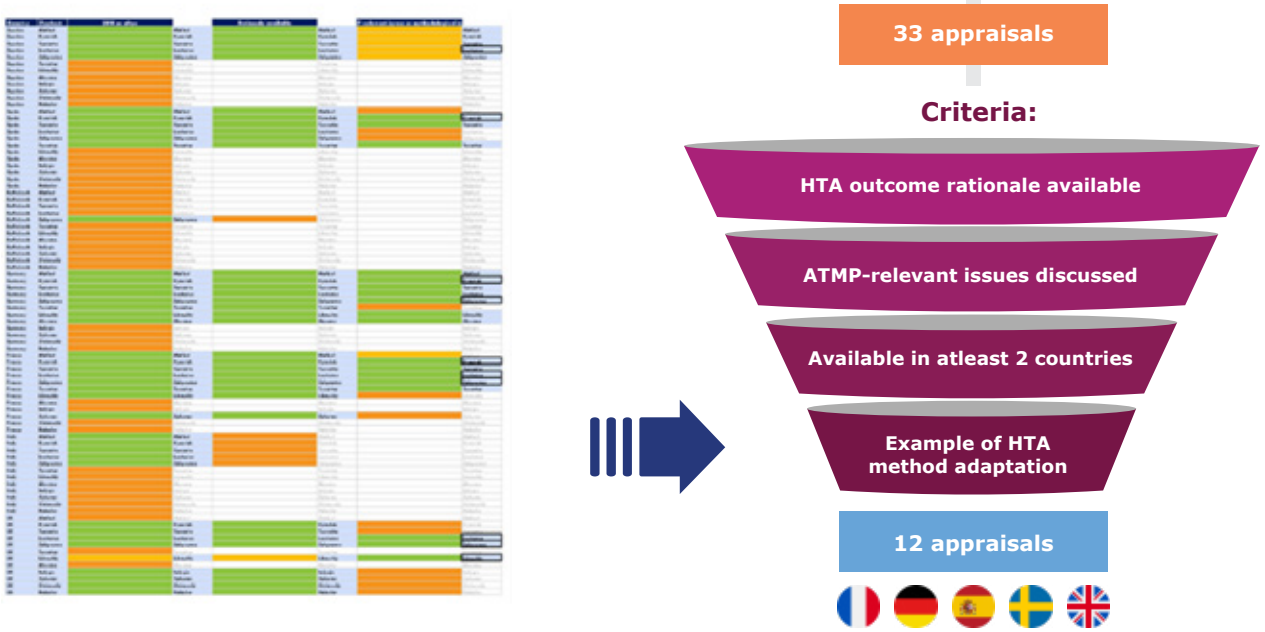
1.1. Background

Following the entry into force of EU Regulation 2021/2282 (Regulation on Health Technology Assessment), Advanced Therapy Medicinal Products (ATMPs) will undergo Joint Clinical Assessment (JCA) starting in 2025. Given this, the Alliance for Regenerative Medicine (ARM) has produced this report to draw lessons learned from recent health technology assessments at the national level.

ARM has conducted a pragmatic review of ATMPs that have been appraised by Health Technology Assessment (HTA) bodies from 2018 in nine European countries: France, Belgium, Luxembourg, Netherlands, Germany, Italy, Spain, Sweden, and the United Kingdom (England and Wales). Following this review, 12 assessments were selected for in-depth analysis (Figure 1). The selection was based on different criteria, including the availability of HTA outcome, the relevance of the ATMP topic discussed the availability of an assessment report in at least two countries, and a demonstration of adaptation of HTA methods.

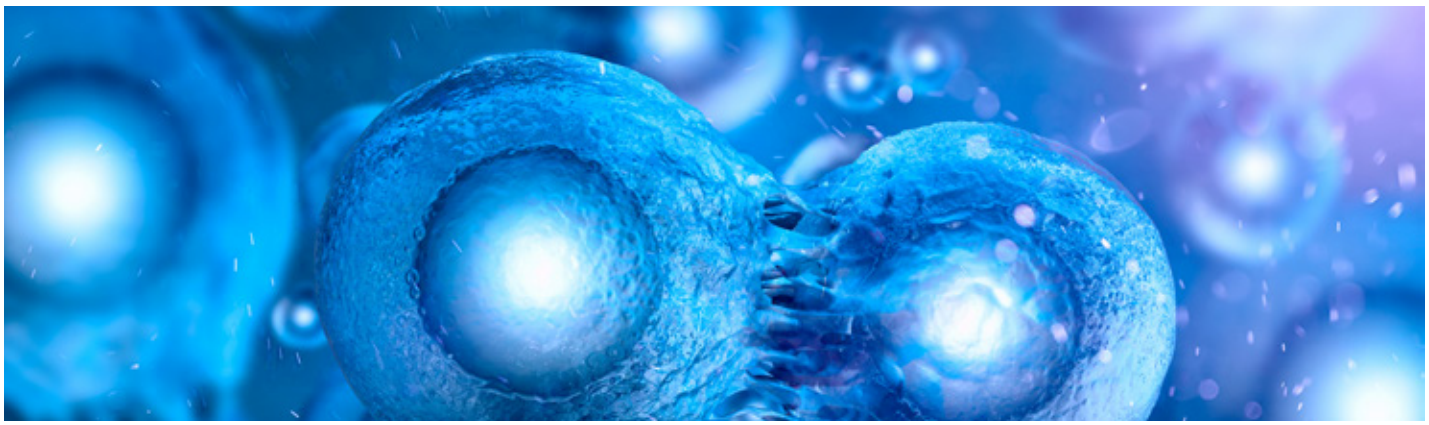
Figure 1

Step-wise approach to identify the most relevant HTA appraisals for review



ARM also reviewed recommended HTA methodology and their updates from the Haute Autorité de Santé (HAS) in France, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, the National Institute for Health and Care Excellence (NICE) in England, and the European Network for Health Technology Assessment (EUnetHTA). Lastly, ARM conducted primary research with seven global industry experts of leading companies developing and commercializing ATMPs, and three HTA experts with wide experience in ATMP assessments

from the United Kingdom, Sweden, and Germany. The UK, Sweden and Germany were selected as countries with publicly available HTA assessments of ATMPs with full rationale underpinning their final recommendations. The expert interviews focused on exploring recent changes to HTA methodologies, challenges that ATMPs face from an HTA assessment perspective, and mitigation strategies. In addition, the potential to address these challenges in the proposed EU JCA methodologies was explored. All findings are presented in this report alongside a set of recommendations.



1.2. ATMP definition and overview of approved ATMPs

In the EU, ATMPs are defined as medicines for human use that are based on genes, tissues, or cells. Recent advances in biomedicine are providing transformative therapy options, particularly for rare diseases and cancers where limited or no alternative treatment options exist, and the unmet need remains high (Horgan et al., 2020).

There are three main types of ATMPs, as defined by the European Medicines Agency (EMA):

Gene therapy medicines:	Contain genes that lead to a therapeutic, prophylactic, or diagnostic effect. They insert 'recombinant' genes into the body. A recombinant gene is a piece of DNA created in a laboratory, comprising DNA from different sources; Gene therapies have the potential to cure a variety of diseases or intercept a disease before patients become symptomatic, including genetic disorders, cancers, and long-term diseases.
Somatic-cell therapy medicines:	Contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose, or prevent diseases.
Tissue-engineered medicines:	Contain cells or tissues that have been modified to be used to repair, regenerate or replace human tissue (EMA, 2020).

As of April 2023, a total of 25 ATMPs have been granted marketing authorization in the EU (EMA, 2023). These products have been approved in 20 different therapy areas, including B-cell acute lymphoblastic leukaemia, lymphoma, and rare inherited disorders, e.g., children with spinal muscular atrophy (SMA) or vision loss due to retinal dystrophy and injury (Table 1).

Table 1 List of current and previously approved ATMPs in the European Union

ATMP	Type	EMA approval	Disease	Manufacture	Status
Hemgenix	Gene therapy	February 2023	Hemophilia B	UniQure & CSL Behring	Conditional approval
Ebvallo	Cell therapy	December 2022	Relapsed or refractory Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ PTLD)	Atara Biotherapeutics	Full approval
Roctavian	Gene therapy	August 2022	Severe Haemophilia A	BioMarin	Conditional approval
Upstaza	Gene therapy	July 2022	Severe aromatic L-amino acid decarboxylase deficiency	PTC Therapeutics	Exceptional circumstances
Carvykti	Gene therapy	June 2022	Multiple Myeloma	Janssen	Conditional approval
Breyanzi	Gene therapy	April 2022	DLBCL – PMBCL -FL3B	BMS	Full approval
Abecma	Gene therapy	August 2021	Multiple Myeloma	BMS	Conditional approval
Skysona	Gene therapy	July 2021	Cerebral adrenoleukodystrophy	Bluebird	Withdrawn in 2021 at the request of the manufacturer
Libmeldy	Gene therapy	October 2020	Metachromatic leukodystrophy	Orchard Therapeutics	Full approval
Tecartus	Gene therapy	October 2020	Mantle Cell Lymphoma	Gilead	Conditional approval
Zolgensma	Gene therapy	May 2020	Spinal Muscular Atrophy	Novartis	Conditional approval
Zynteglo	Gene therapy	June 2019	Beta-thalassemia	Bluebird bio	Conditional approval
Luxturna	Gene therapy	March 2019	Retinal dystrophy	Spark therapeutics	Full approval
Yescarta	Gene therapy	August 2018	B-cell lymphoma	Kite Pharma	Full approval
Kymriah	Gene therapy	August 2018	B-cell ALL and DLBCL	Novartis	Full approval
Alofisel	Cell therapy	March 2018	Perianal fistulas in Crohn’s disease	TiGenix	Full approval
Spherox	Tissue-engineered	May 2017	Cartilage defects in the knee	CO.DON	Full approval

ATMP	Type	EMA approval	Disease	Manufacture	Status
Zalmoxis	Cell therapy	June 2016	Stem cell transplantation for blood cancer	MolMed	Conditional approval
Strimvelis	Gene therapy	April 2016	ADA-SCID	GSK	Full approval
Imlygic	Gene therapy	October 2015	Melanoma	Amgen	Full approval
Holoclar	Tissue-engineered	March 2015	Limbal stem cell deficiency in the eyes	Chiesi	Conditional approval
Provenge	Cell therapy	October 2013	Metastatic prostate cancer	Dendreon	Withdrawn in 2015 at the request of the manufacturer
MACI	Tissue-engineered	July 2013	Cartilage defects in the knee	Vericel	Withdrawn in 2014 at the request of the manufacturer
Glybera	Gene therapy	November 2012	Lipoprotein lipase deficiency	UniQure	Withdrawn in 2017 at the request of the manufacturer
ChondroCelect	Tissue-engineered	November 2009	Cartilage defects	TiGenix	Withdrawn in 2016 at the request of the manufacturer

1.3. Differences between ATMPs and conventional medicines

Medicines can be distinguished into three categories: small molecules, biologics, and ATMPs. Small molecules are chemically synthesized, while biologics are produced using living cells. Although ATMPs could be defined as biologics, they have distinct characteristics that are different from conventional medicines, especially in aspects associated with their clinical development and manufacturing. Some aspects are:

- Generally, small-sized single-arm pivotal clinical trials with distinct patient populations;
- Uncertainties associated with clinical trial design and duration compared to the proposed value proposition;
- Specialised requirements for manufacturing and treatment administration;
- Potential for life-long clinical benefit from a single administration;
- Post-authorization requirements for ongoing demonstration of efficacy and safety;

We have classified the differences between ATMPs, and traditional medicinal products based on the five elements of the PICOS framework (Table 2). The study design parameter includes additional concepts that might differentiate ATMPs from conventional medicines, including the low statistical power of the clinical trial, the absence of comparative data, and the duration of follow-up.

Table 2 ATMPs vs conventional medicines across PICOS parameters

Parameters	Key point	ATMPs vs traditional medicine
Population	Small sample size	The majority of ATMP studies conducted have targeted rare and ultra-rare diseases, evidenced by 15 out of 19 ATMPs with EMA marketing authorisation having orphan drug designation as of August 2022. As a consequence, studies have generally small sample sizes. For example, 22 and 29 children were included in the onasemnogene abeparvovec phase III and atidarsagene autotemcel phase I/II paediatric trials, respectively. HTA bodies may restrict the use of ATMPs to patient populations they consider represented in the trial population. For example, HAS did not recommend the reimbursement of onasemnogene abeparvovec for patients with three copies of the SMN2 gene due to a perceived lack of data in this patient population, despite this group being covered by the EMA label.
Intervention	Treatment timing	Depending on the condition, gene therapies should ideally be administered when patients are pre-symptomatic before the pathology becomes irreversible. For example, pre-clinical data for a gene therapy approach to treat mucopolysaccharidosis type IIIA demonstrated the benefit of earlier intervention. The importance of treatment onset timing has also been seen with onasemnogene abeparvovec in spinal muscular atrophy and atidarsagen autotemcel for metachromatic leukodystrophy (Gray, 2016). Given the need for administration at a very young age, the treatment-eligible population for some ATMPs may be much smaller than the full prevalent population, potentially limited to the incident population only. In addition, given the narrow window for treatment, controlled trials may be unethical or unfeasible for ATMPs in such indications. Another factor to be taken into account is the time between cell harvest, manufacture, and re-infusion (especially in the case of ex-vivo), with potential deterioration of the patient's condition during that period (Gray, 2016).
	Specialised manufacturing processes	The manufacture of autologous cells and tissue therapies requires a complex logistics process. This involves plasma apheresis procedures, followed by the shipment of cells to a manufacturing facility and the subsequent return of the modified cells to the treatment centre. Adding to the complexity, this is dependent upon the availability of manufacturing slots, as seen with the CAR-T and other ex-vivo therapies (Lee, 2018, Magrelli et al., 2020). In vivo manufacturing techniques are equally complex.
	Distinct value proposition and high upfront cost	ATMPs are typically administered once- or twice-only, unlike conventional medicines, which generally require long-term administration. Consequently, ATMPs have a distinct value proposition and therapeutic rationale in relation to their potential comparators. This s value proposition has often been associated with high upfront costs presenting decision-makers with a greater financial risk than conventional medicines, despite a similar or lower overall budget impact than treatments for larger populations (Ronco et al., 2021).
	Specific administration requirements	Ex-vivo ATMPs typically have short half-lives (e.g., 24 to 96 hours) with specific storage and transportation requirements. Delays and

Parameters	Key point	ATMPs vs traditional medicine
		Delays and errors in manufacturing and handling may have irreversible consequences and the loss of treatment opportunities for the patient (Zobel and Heelan, 2017). ATMPs are frequently developed for indications with high unmet needs and disease progression, and patient deterioration may occur during manufacture resulting in patients becoming unsuitable for the demands of the treatment, especially when intensive conditioning regimens are required for the administration of ATMPs (Zobel and Heelan, 2017).
Comparator	Absence of comparative data	ATMPs are typically developed for indications with very limited or no alternative treatment options. Consequently, there are often significant ethical and feasibility issues when studies utilize placebo or less effective comparators; challenges include recruitment, dropout, and blinding (Millum and Grady, 2013).
	Limited feasibility for indirect comparisons	Conducting indirect treatment comparisons can also be challenging with ATMPs, given patient heterogeneity and small patient numbers in different trials and data sources (Mercuri et al., 2018, NICE, 2020). If specific clinical characteristics or biomarkers define the target populations for ATMPs, data on these may not be available in comparator studies. This introduces potential uncertainty in the comparability of the patient populations.
Outcomes	The magnitude of clinical benefit	The objective of ATMPs is two-fold: either providing a lifelong clinical benefit or restoring the patient to the same health as the general population without the disease and benefiting the patient by changing the trajectory of the disease compared to natural history. However, for many therapy areas where ATMPs are developed, there may be no universally accepted definition for "cure" or "remission" or a minimal clinically significant difference for key outcomes. Additionally, the definition of the benefit duration may vary, presenting a complication for contracting and retreatment decisions. This makes it hard to define a significant or transformative treatment effect. Trial outcomes must be accepted by multiple stakeholders to be considered innovative and justify investment in the acquisition and delivery of costly and complex ATMPs. Some ATMPs have the potential to cure disease rather than only treat its symptoms, transformative benefits that are often not possible with traditional pharmaceuticals (Alliance for Regenerative Medicine, 2019). The extent of ATMPs' value to patients, families, and caregivers depends upon the product and disease in question. ATMPs have already delivered significant value to patients suffering from a range of life-threatening conditions, many caused by genetic mutations (Alliance for Regenerative Medicine, 2019).
	Surrogate outcomes for long-term clinical benefit	ATMPs could address the underlying cause of the disease, resulting in long-term clinical benefits. However, it is not feasible to demonstrate a potential lifetime clinical benefit within the context of a registrational study. In addition, given the frequent high unmet need, the long duration of studies would be unethical as it would delay access. Therefore, manufacturers must use interim or surrogate endpoints to measure clinical benefit within the context of a clinical trial. However, for HTA bodies and payers, the use of surrogates for the long-term clinical benefit may be associated with significant uncertainty around

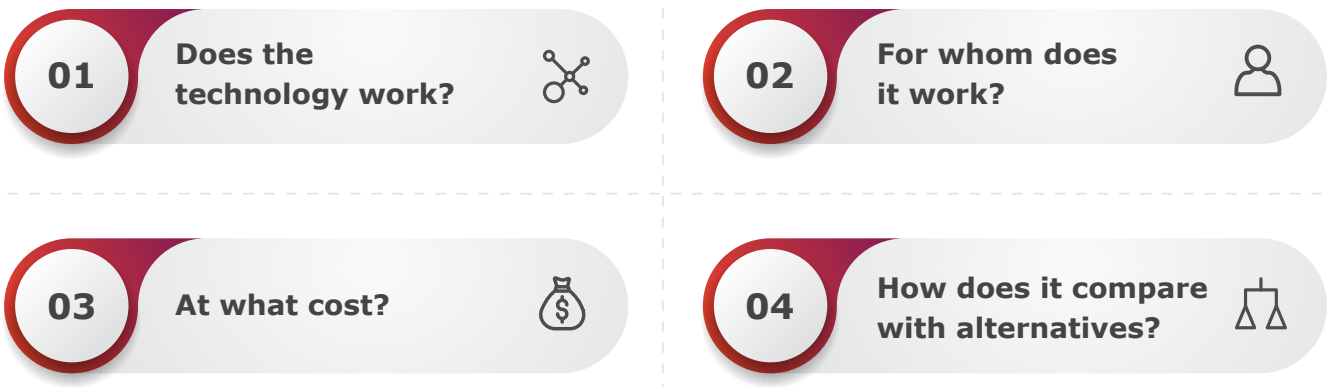
Parameters	Key point	ATMPs vs traditional medicine
		treatment durability. Given the high upfront cost of ATMPs, reflecting the anticipated value of the long-term clinical benefit, HTA bodies may consider the uncertainty regarding the durability of the effect unacceptable (Ronco et al., 2021).
Study design	Low statistical power and non-alignment of endpoints	ATMPs may be investigated in small study populations for practical reasons. Such studies may be powered for primary endpoints that support regulatory approval instead of clinical endpoints preferred by payers and HTA bodies. Additionally, these smaller trials may lack statistical power to inform assessment in subgroups considered relevant in routine clinical practice. For example, in the appraisal of betibeglogene autotemcel, the NICE ERG identified the underrepresentation of patients with specific genotypes in the trial population as an issue during the technical engagement. The NICE Appraisal Committee considered this a source of uncertainty when considering the generalisability of the trial population to routine clinical practice.
	Unblinded design	The unique formulation and complex administration associated with ATMPs makes effectively blinding studies infeasible, even when a randomized controlled trial may have been intended. For example, it would be infeasible to conduct a blinded study of an ex vivo therapy. The absence of blinding can introduce uncertainty in the assessment of subjective outcomes, such as clinician and patient-reported outcomes and HRQoL. This perceived uncertainty may lead to HTA bodies undervaluing the benefits of ATMPs to patients.
	Duration of follow-up	Regulatory bodies require long-term clinical monitoring and follow-up of patients who receive gene therapies as part of post-marketing commitments, with the extent of follow-up dependent on the type of intervention, route of administration, and patient population. Such post-marketing commitments are considered essential to validate the long-term safety and efficacy profile of the products. Manufacturers are required to describe the post-marketing studies in the marketing authorization application and the specific risks and risk management plans required (BIOREG, 2016).
Evidence outside the clinical trial	Post-authorization evidence needs	Real-World-Data (RWD) derived from registries and other sources such as electronic health records, medical databases, and post-authorization studies have been used to support the efficacy and safety claims of ATMPs. Natural history data can provide a synthetic control arm for situations where RCTs are not feasible (Jonsson et al., 2019, Iglesias-Lopez et al., 2021). RWD has strong potential to complement evidence gaps and address uncertainties, but national HTA bodies and EUnetHTA are reluctant to adopt methods and processes incorporating RWD.

2. Health Technology Assessment methods and their potential challenges for ATMPs

- JCA methods proposed by EUnetHTA21 are unable to capture the entire value proposition for ATMPs
- General challenges limiting access to ATMPs can be related to legislation, manufacturing, data generation, HTA, pricing, and funding.
- Specific examples are reported illustrating the HTA challenges that ATMPs have faced in some European countries, such as in Germany, to demonstrate an added benefit in a patient-relevant endpoint versus the appropriate comparator therapy, and in England and Wales in relation to the cost-utility analysis.

2.1. Introduction to Health Technology Assessment

HTA is the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of a technology, as well as its indirect and unintended consequences, to inform decision-making (NIHR). This multidisciplinary process uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making to promote an equitable, efficient, high-quality health system (O'Rourke et al., 2020). In what is now considered a classical paper, Hutton et al. defined the four key questions HTA addresses (Hutton et al., 2006):



More recently, EUnetHTA has developed a methodological framework for the collaborative production and sharing of HTA information and has identified nine domains of information relevant for HTA decision-making (EUnetHTA, 2016):

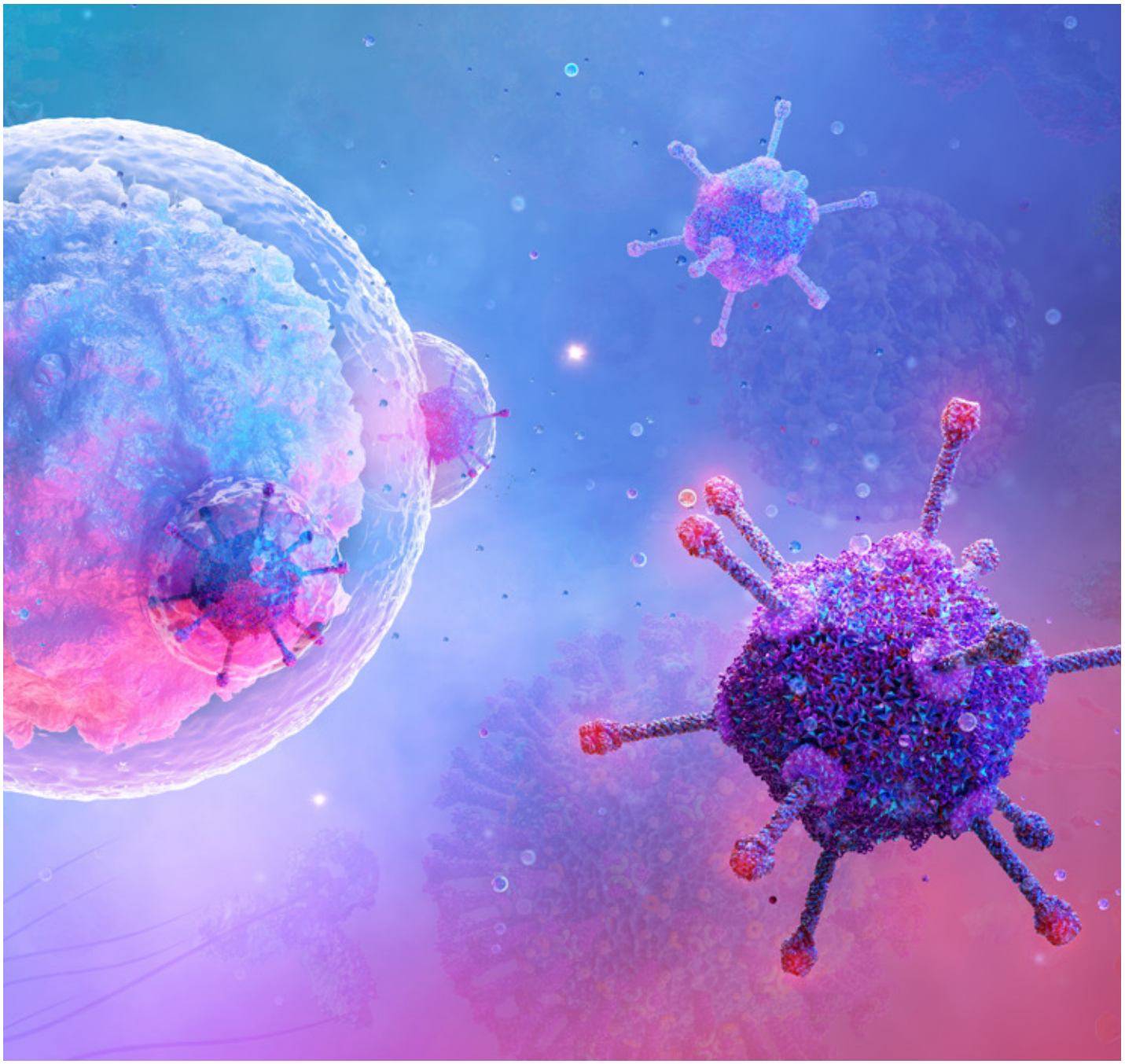
These assessments and appraisals are used by health systems in various ways. HTA bodies may help determine the price or conditions applied to reimbursement, aid in market access decisions on the degree and mechanism of funding or provide guidance for physicians and patients in the form of treatment guidelines.

2.2. Challenges for ATMPs

There is evidence that traditional HTA methodology does not adequately capture the entire value proposition for ATMPs, which have the potential to 'cure' rare or ultra-rare diseases. It should also be considered that if the lifelong benefit potential of ATMPs were captured, HTA bodies and payers would be willing to accept a higher level of uncertainty in their decision-making for treatments that could be genuinely transformative for patients. (Qiu et al., 2022). HTA methods were initially developed to assess and appraise new medicines compared to existing treatments using data from randomised clinical trials (RCTs) to demonstrate comparative clinical and economic value from a healthcare system perspective.

HTA methods were designed for conventional, non-personalized medicines and did not anticipate the transformative benefit of ATMPs. For example, ATMPs may provide additional value beyond comparative effectiveness, which is shaped by the contextual considerations of the therapeutic area (e.g., the severity of the condition, availability or anticipated availability of other treatments, ethical priorities), and additional benefits or disadvantages (Salzman et al., 2018).

Following regulatory approval, several ATMPs have been appraised by national HTA bodies (see Figure 1). These appraisals provide early insights into the opportunities and challenges for these innovative therapies.



2.2.1. Overview of patient access challenges with ATMPs

ARM previously researched general challenges for ATMPs from the viewpoints of manufacturers and stakeholders (Alliance for Regenerative Medicine, 2019) and discovered five key themes:

Legislative challenges:

Custom-made ATMPs prepared in a hospital for a specific patient can be regulated via the Hospital Exemption (HE) (Article 28 of Regulation 1394/2007/EC), which provides an exemption from the EMA's centralized procedure for authorization. However, there is a lack of clarity on the HE definition, given the vague terminology used in the legislation. This may lead to safety and quality issues and create unfair competition to EMA-authorised ATMPs by decreasing the market size and potential return on investment (Corbett et al., 2017, Alliance for Advanced Therapies, 2013).

Manufacturing challenges:

The specific regulatory requirements for the manufacture of cell and gene therapies require complex processes and supply chains. This leads to high costs in facilities and staff and can pose a challenge to scaling up ATMP therapies (Kent and Spink, 2017, Macaulay, 2017).

Data generation challenges:

While the clinical development requirements applied to ATMPs are similar to other products, it may not always be possible for manufacturers to carry out "gold standard" RCTs, given the lack of appropriate comparators and ethical concerns. Blinding may also be unfeasible, given the complex administration procedures for ATMPs. In addition, the patient population in ATMP studies is typically small, posing a barrier to the generation of robust clinical data on efficacy and safety exacerbated by the added complexity of demonstrating the durability of effect in the long term (Abou-El-Enein et al., 2016, Corbett et al., 2017, Macaulay, 2017).

HTA and access challenges:

ATMPs may reach the market with insufficiently mature clinical data due to the data generation challenges highlighted above, leading to high uncertainties for HTA assessments of value. In addition, due to the relatively high prices often required by ATMP manufacturers, the evidence presented is subjected to more intense scrutiny by HTA bodies and payers. The issue for HTAs is balancing what may be a significant step forward for patients with the uncertainty they have about the value and the opportunity cost the treatment may have for others (Abou-El-Enein et al., 2016, Carr and Bradshaw, 2016, Crabb and Stevens, 2016).

Pricing and funding challenges:

Payers and other stakeholders consider ATMPs costly, leading to affordability issues. Various payment models have been suggested, including financial-based and outcomes-based agreements with variable adoption across different countries (Alliance for Regenerative Medicine, 2019). However, there remain obstacles to the full uptake of innovative contracting and pricing solutions to mitigate the affordability and sustainability challenges arising from the high costs of ATMPs.

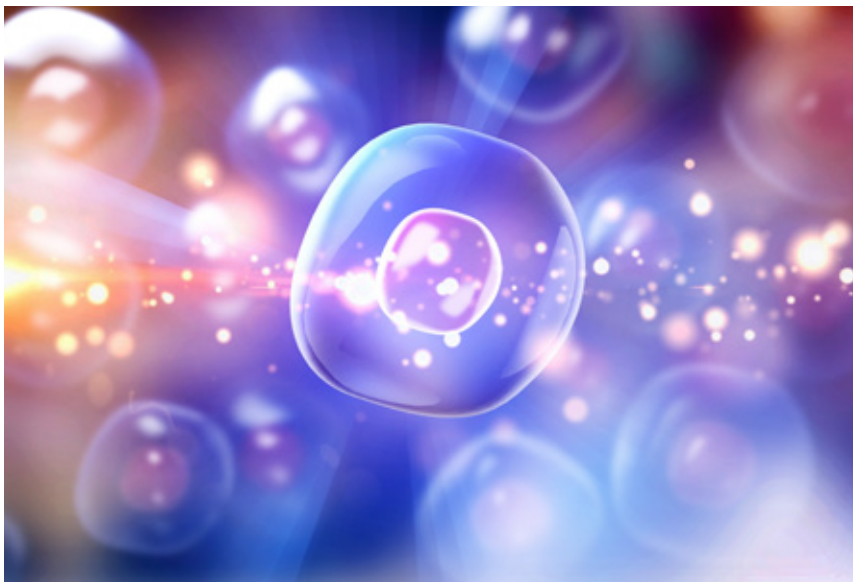
2.2.2. Examples of ATMP appraisal challenges by European HTA bodies

In this section, we summarize the issues identified during our review of ATMP appraisals, discuss some of the key challenges identified regardless of the HTA methods, and categorize these according to the domains of the PICO framework. We illustrate examples of appraisal challenges for two ATMPs assessed in Germany and for three in England and Wales. In Germany, the challenges of demonstrating additional benefit based on indirect comparisons are described, whereas, for England and Wales, the complexity of demonstrating cost-effectiveness is explored.

Germany

In Germany, a full benefit assessment requires the manufacturer to demonstrate an added benefit in a patient-relevant endpoint versus the appropriate comparator therapy. While a direct comparison within an RCT is preferred, an adjusted indirect comparison via an appropriate common comparator may be accepted.

Although indirect comparisons are associated with increased uncertainty and risk of bias, they may be acceptable for facilitating the interpretation of the added benefit relative to the appropriate comparator therapy for an early benefit assessment (IQWiG, 2021). While these methods have been accepted in prior appraisals, the perceived uncertainty and risk of bias have limited the extent of added benefit.



Overall, the high standard for comparative evidence against an appropriate comparator presents a major challenge for ATMPs to demonstrate an added benefit rating higher or less than **'unquantifiable added benefit.'**

For the early benefit assessment of axicabtagene ciloleucel, the manufacturer conducted indirect comparisons between the single-arm study ZUMA-1, the retrospective SCHOLAR-1 study, and 15 published studies. The indirect comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel for the overall survival endpoint. However, given the disease's poor prognosis and non-comparability of study populations, the added benefit of axicabtagene ciloleucel was recognised as non-quantifiable by G-BA.

The manufacturer performed an indirect comparison between ZUMA-1 and SCHOLAR-1, a retrospective study including data from two observational studies and the follow-up of two RCTs. Despite issues with the indirect comparison, the G-BA accepted the observed survival benefit due to the poor prognosis and advanced stage of the disease. Patient-level data were available, which allowed a comparison between the patient characteristics of the study populations in ZUMA-1 and SCHOLAR-1. Revisions to the indirect comparisons were requested by the G-BA to exclude patients with features that were deemed inconsistent with the ZUMA-1 patient population. These changes led to the indirect comparison being accepted by the G-BA

and to an unquantifiable added benefit rating, despite some uncertainty due to incomplete patient data in part of the analysed population.

In contrast to the indirect comparison to the SCHOLAR-1 study, the indirect comparison between ZUMA-1 and the 15 published studies was not accepted for the benefit assessment. The patient populations in the 15 studies were not considered comparable with the ZUMA-1 study population due to either a lack of detail in the publications reporting patient characteristics or actual relevant differences between the patient characteristics of the studies.

While the abridged benefit assessment for orphan drugs allows manufacturers of ATMPs to receive an added benefit rating without conventional comparative clinical evidence, this presents challenges for ATMPs that exceed the €50 million budget threshold, which has recently been lowered to €30 million.

When the pivotal trials of onasemnogene abeparvovec were initiated in 2017, there was no approved therapy for SMA, making an RCT infeasible and unethical. Additionally, with only a limited number of small and heterogenous studies available, conducting an appropriately matched and adjusted indirect comparison was challenging.

Initially, the early benefit assessment of onasemnogene abeparvovec was conducted using the abridged assessment specific for orphan drugs. However, this assessment was terminated after the sales of onasemnogene abeparvovec exceeded the €50 million budget threshold. The manufacturer was subsequently required to resubmit a full dossier with evidence of additional benefit versus an appropriate comparator therapy.

The G-BA considered nusinersen as the appropriate comparator therapy. However, the clinical development of onasemnogene abeparvovec was based on single-arm studies, with no RCTs for a direct or adjusted indirect comparison. Additionally, the patient populations for the onasemnogene abeparvovec and nusinersen studies had significant differences in disease duration and criteria for ventilation and respiratory symptomatology. These were considered significant confounders and sources of uncertainty. This uncertainty meant the G-BA did not accept the indirect comparisons for the benefit assessment.

England and Wales

In England and Wales, NICE technology appraisal committees are willing to accept a broader range of clinical evidence, including RWE and indirect treatment comparisons. Additionally, the recently updated NICE methods allow appraisal committees to accept greater uncertainties in challenging therapeutic areas, acknowledge situations where treatment benefits are not captured within the economic analysis, and consider the broader benefits of innovative treatments on the NHS (NICE, 2022).

However, despite the flexibility in the NICE methods, conducting a cost-utility analysis of a new treatment can be challenging, especially for ATMPs. There are three main reasons for this, which include: capturing the true decrement in HRQoL and health utility, valuing the long-term benefits of treatments with high upfront costs, and uncertainty in the duration of clinical benefit.

NICE prefers EQ-5D-3L to measure HRQoL and derive health utility values. However, generic HRQoL preference-based measures such as the EQ-5D may not capture the full deterioration in HRQoL experienced by patients with rare diseases (Efthymiadou et al., 2019). This means the required cost-utility analysis does not capture the true deterioration in HRQoL and health utility, leading to an underestimation of the QALY gain associated with new treatments.

Whilst the NICE Health Technology Evaluations manual describes the use of alternative sources of utilities to the EQ-5D, this requires stringent evidence. The NICE Health Technology Evaluation manual states that the manufacturer must demonstrate a lack of content validity, poor construct validity, and responsiveness (NICE, 2022). In some instances, EEQ-5D-derived utilities remained the appraisal committee's preferred source of utility data despite being acknowledged as unsuitable, for example, in the HST appraisal of voretigene neparvovec (NICE, 2019).

The use of the NICE reference case discount rate of 3.5% also presents challenges for ATMPs, which are usually indicated for slowly progressing disease and are associated with high upfront costs and long-term health benefits lasting well beyond the duration of the trial and treatment. The NICE methods guide states that the committee has the discretion to use a non-reference case discount rate of 1.5% if there is a highly plausible case for the maintenance of benefits over time. However, the requirements for use are stringent and are limited to technologies for people who would otherwise die or have a very severely impaired life, for technologies that are likely to restore patients to full or near-full health, and for therapeutic benefits that are likely to be sustained over a very long period (NICE, 2022, NICE, 2013).

In the HST appraisals of voretigene neparvovec and onasemnogene abeparvovec, the NICE appraisal committees were uncertain about the suitability of the 1.5% discount rate in both cases, despite the biological plausibility of a durable clinical benefit, and stated both the 1.5% and 3.5% discount rates should be used to inform decision making.

ATMPs offer the potential for long-term treatment benefit in many patients with severe disease and limited treatment options. However, for manufacturers of these advanced therapies, it is often not feasible to provide evidence of a sustained treatment effect of five to ten years in sufficient numbers of patients to mitigate this uncertainty completely.

During the appraisal of betibeglogene autotemcel, for example, follow-up data were available from only 24 patients with a maximum duration of 61 months, despite a planned 15-year follow-up. The available follow-up data were considered insufficient to demonstrate durable clinical benefit in excluding the risk of late engraftment failure or disease relapse.

2.2.3. HTA challenges for ATMPs mapped to the PICOS framework domains

We selected 12 HTA appraisals in Europe based on the following criteria: (i) selected appraisals from the year 2018 containing ATMP-relevant issues; (ii) HTA report availability in at least two countries, and (iii) examples of HTA method adaptation. We identified trends and several key issues common across ATMPs in the 12 appraisals that were reviewed (AEMPS, 2019b, AEMPS, 2019a, G-BA, 2019b, G-BA, 2019a, G-BA, 2020b, G-BA, 2020a, G-BA, 2021b, G-BA, 2021c, HAS, 2019b, HAS, 2019a, HAS, 2019c, HAS, 2020a, HAS, 2020b, HAS, 2021a, HAS, 2021d, HAS, 2021c, NICE, 2019, NICE, 2021, TLV, 2019). These were validated and expanded following industry and HTA expert interviews. The challenges identified are shown in Table 3, following the PICO framework previously presented:

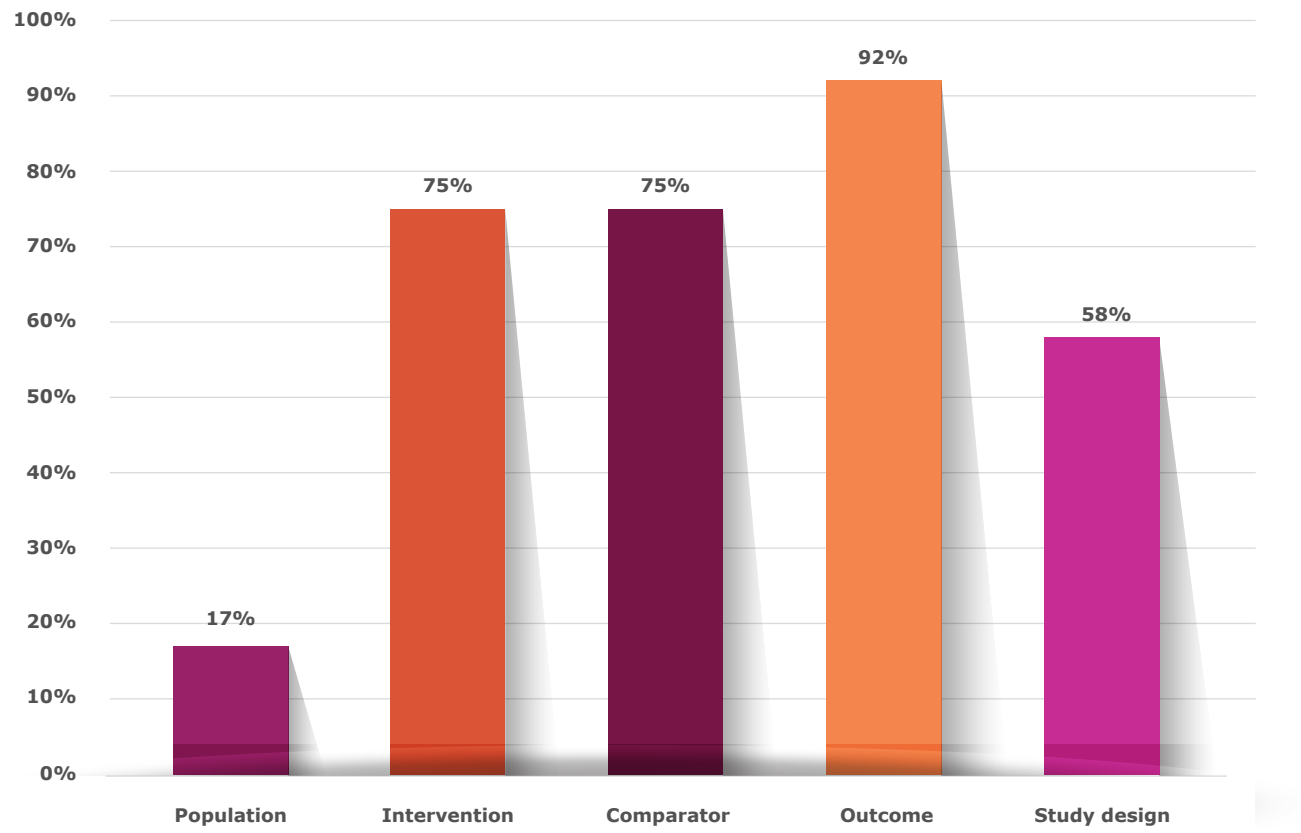
Table 3 Key challenges for ATMPs at the time of HTA appraisal

Parameters	Key issues	Details and examples
Population	Potential lack of generalisability of the study population to real-world practice	In their assessment of voretigene neparvovec, TLV highlighted that the pivotal trial included a **small number of patients** (total of 31 participants) and the study **only included patients with congenital amaurosis type 2**, whereas the marketing authorization was granted to a broader category of patients with RPE65 mutation. Despite these challenges, TLV noted that the small population was expected due to the rarity of the disease and that treatment benefits could be expected for all patients with RPE65 mutation, as per the opinion of TLV's clinical experts (TLV, 2019). In Germany, in their assessment of tisagenlecleucel, the G-BA highlighted the issue pertaining to the **generalisability of study data** to the German population, given that only one publication was used to determine the incidence of DLBCL in the German population, leading to uncertainty.
Intervention	Issues arising from the administration of the ATMP	HTA bodies have previously highlighted the **difficulties of administration** of ATMPs in a real-world setting. For example, in their assessment of voretigene neparvovec, TLV highlighted the concerns on extrapolation of dose administration to local healthcare systems, which could lead to a greater incidence of complications compared to administration in fewer and more specialised centres (TLV, 2019). These challenges can also lead to p**atients no longer being eligible for treatment** due to longer waiting times related to delays in the diagnosis and for the product to be manufactured. For example, the G-BA highlighted the potential for patient discontinuation due to longer waiting times in their appraisal of **tisagenlecleucel** for DLBCL and, consequently, highlighted that study results carried a risk of distortion.
Intervention	Criticism around the lack of comparative data and difficulties in	G-BA noted that the studies submitted for **tisagenlecleucel** in B-cell ALL were non-comparative and open-label and therefore carried a **high risk of bias**. Further, the G-BA noted that **no sufficiently valid**

Parameters	Key issues	Details and examples
	carrying out indirect comparisons	**conclusions** on the extent of the added benefit could be derived on the basis of indirect comparisons due to the difficulty in determining long-term benefits from the trials and uncertainties regarding the comparability of studies.
Outcomes and Study Design	Uncertainties related to the sustainability of the clinical benefit over time	While assessing **voretigene neparvovec**, NICE noted that the company had assumed a 40-year treatment effect. This was meant to represent a reasonable midpoint between a minimum of 7.5 years of follow-up and a potential maximum of around 70 years. The committee noted that the evidence available was limited to 3 to 4 years and considered that assuming a long-term treatment effect **was associated with substantial uncertainty,** despite recognizing that the therapy would likely provide long-term benefits.

Analysis of the HTA challenges across the PICOS elements identifies the key areas of focus for manufacturers (Figure 2).

Figure 2 Percentage of HTA issues per PICOS category



3. Recent HTA changes and initiatives at the EU and country level

- The innovative nature of ATMPs presents challenges in the most appropriate way to assess their clinical and cost-effectiveness, given the diseases they target and the characteristics of the interventions. The willingness of HTA bodies to accept a greater level of uncertainty will be key to allowing a more flexible HTA assessment.
- A brief comparative overview of HTA methods is reported at the European level and in selected countries using the PICOS framework.
- Recent changes in HTA methodology have been reported in some countries. In England, the severity modifier has been introduced that provides a higher cost-effectiveness threshold for treatments that meet specific criteria, and in France there is new guidance on best practices for RWE generation.

3.1. HTA methods at the EU and country level

As highlighted in the previous section, the characteristics of ATMPs present challenges in the most appropriate way to assess their clinical and cost-effectiveness. Despite these, several ATMPs have been recommended by HTA bodies. A common feature ARM has observed across these recommendations has been the willingness to accept a greater level of uncertainty in the clinical and economic evidence and to flexibly adapt HTA methods for the appraisal of these innovative therapies.

ARM has reviewed the current HTA methods for the HAS, NICE, G-BA/IQWiG, and EUnetHTA according to the PICOS framework and to identify recent trends in HTA methodology updates that could impact future ATMP appraisals (Table 4). ARM has also reviewed recent methodological updates and their potential implications for ATMPs (Table 5).

In addition to the secondary research, the team has discussed recent trends and changes with several industry and HTA experts, who have described successful case studies of processes during which HTA bodies have adapted their appraisal methods or have been more flexible in their approach in their appraisals of ATMPs.

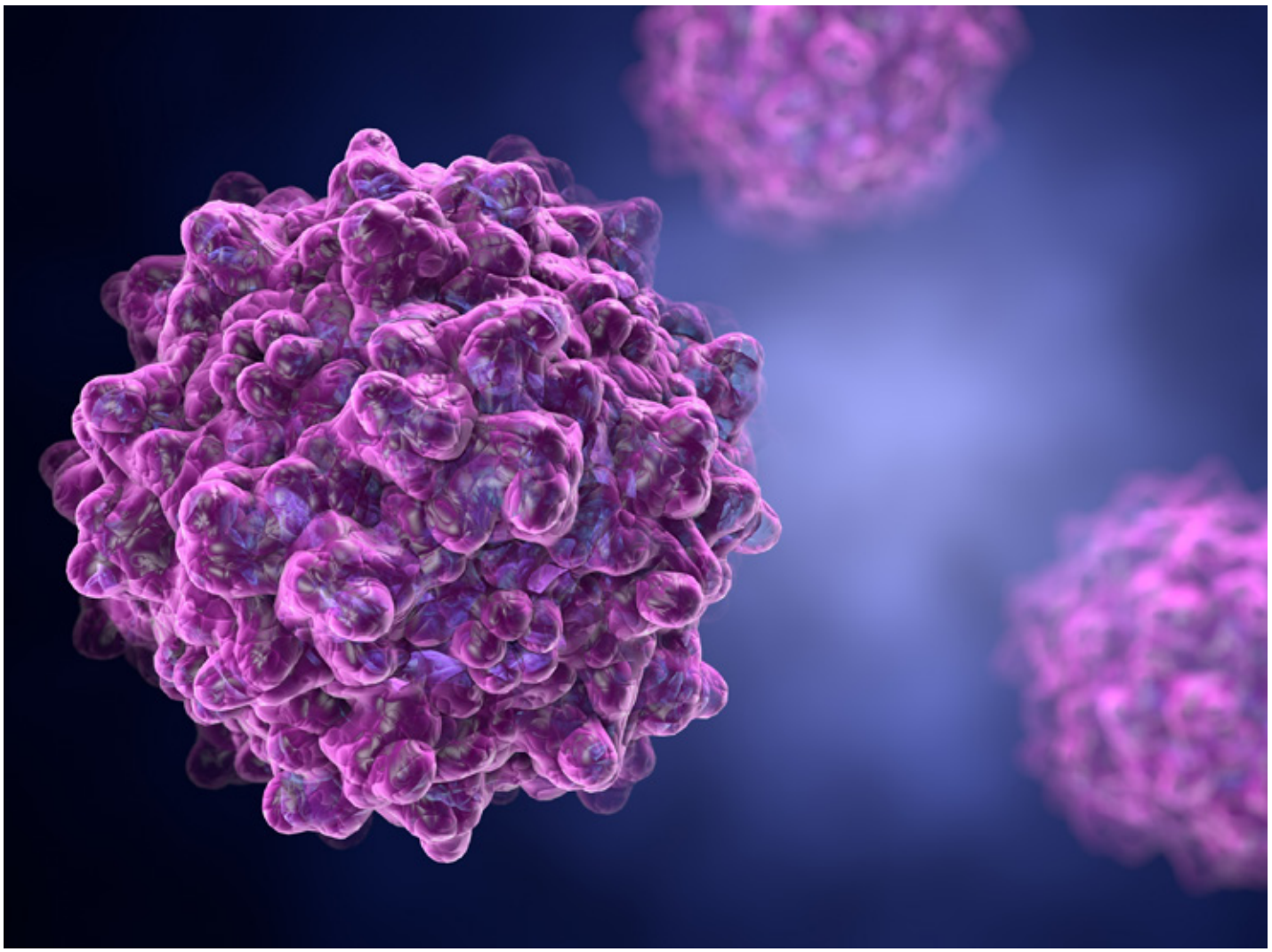
Based on the primary and secondary research, ARM has highlighted how different HTA bodies have managed perceived uncertainties based on the submitted evidence for recent ATMP appraisals and the implications for HTA decision-making (Table 5). We have also included a summary of the remaining challenges for the appraisal of ATMPs.

Table 4 Brief comparative overview of HTA methods across EU and country level

PIOCOS domain	HAS	NICE	IQWiG/G-BA	EUnetHTA
Population	Determination of the target population eligible to receive the reimbursed health technology is based on available epidemiological data and effects of existing treatments.	The population(s) will be informed by the indication and care pathway. Relevant subgroups may include people for whom the clinical or cost-effectiveness might differ or groups who need special consideration.	The population for benefit assessment is based on the labelled indication. Pre-specified subgroup analysis can investigate possible heterogeneity in treatment effect.	The relevant population(s) should be based on the indication and the local healthcare situation and should either be the full population and/or subpopulation(s) of the full population.
Intervention	The intervention is the medicinal product, in the indication assessed, based on the manufacturer's dossier.	The intervention is the health technology undergoing evaluation in the anticipated positioning in the NHS.	The benefit assessment of a drug according to §35a SGB V is based on a dossier submitted by the manufacturer.	The intervention is the health technology assessed in the indication described in the regulatory submission.
Comparator	A clinically relevant comparator may be a health technology (medicinal therapy, medical device, procedure, or non-medicinal therapy) that plays the same role in the therapeutic strategy and patient population. For health economic evaluations, comparators used in routine practice are most often used. Health technologies subjected to an early access program or routine off-label use may be considered relevant for comparison.	The Appraisal Committee may identify the most appropriate comparator from all relevant comparators identified during scoping. Off-label comparators are considered relevant if they are established in routine clinical practice in the NHS. Technologies recommended within managed access are not considered part of routine commissioned care and, consequently, are not suitable comparators.	Appropriate comparator therapy must be an appropriate therapy in the indication in accordance with the recognized standard of care. The comparator must have regulatory approval in the therapeutic area, and non-drug comparators must be suggested by the statutory health insurance system. Comparators with demonstrated patient-relevant benefit are preferred.	Comparator(s) could be approved or off-label in the EU. Pharmacotherapy, medical devices, and non-drug interventions are appropriate comparators. Prior guidance stated that the ideal comparator should be the reference treatment according to European or international clinical guidelines or be used routinely in clinical practice and validated for the clinical indication.
Outcomes	The primary outcome of a study must be a relevant clinical endpoint wherever it is	Relevant outcomes include any health outcomes resulting directly or indirectly from any technologies	The early benefit assessment is based on patient-relevant endpoints, mortality, morbidity, and HRQoL.	All clinical endpoints should be comprehensively defined and justified in the

PIOCOS domain	HAS	NICE	IQWiG/G-BA	EUnetHTA
	possible to collect one. The use of a surrogate endpoint is acceptable if a link with a clinical endpoint for mortality or morbidity has been demonstrated in the concerned disease. The use of a surrogate endpoint (without demonstrating a link with a relevant clinical endpoint) may be considered in the assessment of the clinical added value (CAV). An improvement in HRQoL may be used to demonstrate CAV when assessed with validated scales appropriate to the objective and with a rigorous methodology.	being evaluated and should measure health benefits and adverse effects that are important to patients and their caregivers. The clinical outcome measures may include quantification of survival or HRQoL that translates into QALYs. Outcomes should be informed by patient engagement. Core outcome sets should be used if suitable based on quality and validity. PRO measures should be validated, and the data collection methods clearly reported.	Other criteria, such as patient satisfaction, may be considered but cannot demonstrate added benefit alone. Certain beneficial aspects may only be assessed if relevant therapeutic effectiveness has been proven, e.g., interventions for a serious or life-threatening disease must improve mortality or serious morbidity. Surrogates are only considered if they have been validated in appropriate patient populations and interventions. PROs may be used to assess HRQoL, symptoms, and treatment satisfaction. PRO data from unblinded studies have limited validity and greater uncertainty.	study protocol(s) and report. These should be clinically relevant to the disease being treated. Clinical endpoints should be long-term or final endpoints where possible, although short-term endpoints are acceptable for acute conditions with no long-term consequences. If surrogate endpoints are used, they should be adequately validated, and extrapolation should be underpinned by a clear biological or medical rationale or a strong or validated link.
Study design	A direct comparison with the clinically relevant comparator within the framework of a double-blind RCT is expected wherever possible. The absence of direct comparison with a clinically relevant comparator must be justified by the company and may be accepted by the TC in certain situations. Indirect comparisons should be conducted using defined and validated methodological principles.	To compare relative treatment effects, high-quality RCTs are preferred. Non-randomised studies may complement RCTs when evidence is limited or from the primary source of evidence when there is no RCT evidence. When comparing technologies that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with an NMA	IQWiG grades the degree of certainty at the individual study and outcome level: • High certainty: a randomised study with a low risk of bias; • Moderate certainty: a randomised study with a high risk of bias; • Low certainty: results from a non-randomized comparative study. The risk of bias is assessed based upon randomization, blinding of subjective outcome assessments (where blinded studies are unfeasible),	Gold-standard evidence on the benefit of treatment over an existing comparator is from adequate RCTs with a low risk of bias. Non-randomized evidence includes single-arm trials, cohort studies, case-control studies, other observational studies, and the use of historical controls. These studies have a greater risk of bias in estimating

PIOCOS domain	HAS	NICE	IQWiG/G-BA	EUnetHTA
	Observational studies may include ATUs, registries, databases, and post-registrational studies. Observational data, especially ATU data, may contribute to the assessment of CB and CAV. However, they cannot substitute for comparative studies where these would be expected or have failed to demonstrate efficacy.	(including adjusted indirect comparisons and mixed treatment comparison) if appropriate. The lack of direct evidence will be associated with additional uncertainty by the Appraisal Committee. The evidence available on a technology and patient population should be integrated into a systematic review.	and application of the ITT principle. The use of indirect comparisons requires adequate justification and are associated with a lower certainty of results. Only adjusted indirect comparisons via appropriate common comparators are accepted.	utilisation relative treatment effectiveness.



Abbreviations: ATU = autorisation temporaire d'utilisation (temporary authorisation (ATU) programme); CAV = clinical added value (ASMR); CB = clinical benefit; ITT = intention to treat; NRS = non-randomized study; PRO = patient-reported outcome; QALY = quality-adjusted life year; RCT = randomised controlled trial

3.2. Recent changes to HTA methods and implications for ATMPs

There have been recent changes in HTA methodology in countries such as the UK (England & Wales) and Germany. These updates aim to simplify and accelerate the appraisal process, recognise disease severity, incorporate RWE, and provide greater flexibility when managing uncertainty:

Table 5 An outline of recent changes in HTA methodology and likely implications for ATMPs

HTA agency	Recent changes	Implications for ATMPs
NICE	**Introduction of a disease severity modifier** A severity modifier allows an Appraisal Committee to apply a greater weight to QALYs for technologies indicated for severe diseases by recommending them at higher cost-effectiveness thresholds. Severity is defined as the future health loss because of the disease or condition with the usual standard of care and may be determined by either the absolute or proportional QALY shortfall: • Absolute QALY shortfall is the future health, including quality and length of life lost, compared with the expected future health people without the condition would have. • Proportional QALY shortfall represents the proportion of future health that is lost because of the condition, which is the absolute QALY shortfall divided by the remaining QALYs that the general population with the same age and gender distribution would be expected to have.	The introduction of a severity modifier provides a higher cost-effectiveness threshold for ATMPs indicated for conditions that meet the severity threshold. Eligible treatments may be considered cost-effective at £36,000-£50,000 per QALY, depending on the extent of the QALY shortfall. This update does not affect the QALY weighting that applies to HST appraisals (QALY threshold of £100,000).
	Greater flexibility in the assessment of uncertainty and the effect on cost-effectiveness Whilst NICE still requires the most robust evidence base possible, committees will have greater flexibility over the decision to accept uncertainties on a case-by-case basis to prevent access barriers to valuable treatments. An anticipated situation where evidence generation may be challenging includes paediatrics, rare diseases, and situations where the new treatment is innovative or complex.	Under the new guidance, NICE will have the flexibility to recommend ATMPs where there is increased uncertainty due to challenges with evidence generation.
	Adopting different approaches to evidence NICE has published an RWE framework, which provides guidance on the planning, methodology, and reporting of RWE to inform HTA, with three key principles for high-quality evidence: • Evidence should be developed in a fully transparent and reproducible way. • Data should be identified through systematic, transparent, and	ATMPs can utilize alternative approaches to evidence generation for both RWE and health utilities where the reference case methods are inappropriate or insufficient.

HTA agency	Recent changes	Implications for ATMPs
	reproducible approaches. • Data should be analysed using appropriate methods, and bias and uncertainty should be fully characterized. NICE has provided further guidance on measuring HRQoL and health utilities in situations where the EQ-5D is unsuitable. Prior guidance from the 2013 Methods Guide on the use of health utilities derived from the literature, mapping functions, and demonstrating that EQ-5D is unsuitable in the target population remains unchanged. However, the updated methods guide now describes NICE's preferred alternative to the reference case methods for measuring HRQoL: • Vignette studies developed according to NICE's preferred methodology. • Utility values from a proxy condition with a similar HRQoL impact derived using reference case methods. • Other generic or condition-specific measures. • Direct valuation of patients' own health.	Clear guidance on suitable alternatives to reference case methods offers improved predictability for health technology developers.
	Changes to the HST programme Several changes to HST routing criteria (small target population, clinically distinct target population, chronic and severely disabling condition) have been introduced, including replacing the term 'ultra-rare condition' with 'very rare condition' and reducing the HST eligibility criteria from seven to four to improve the efficiency, predictability, and clarity of the HST selection process.	Revisions to the HST programme may allow more eligible ATMPs to potentially benefit from the HST appraisal process, with its specific methods for rare conditions and flexibility for the higher cost-effectiveness thresholds.
	Innovative Licensing and Access Pathway ILAP is a new pathway supporting innovative approaches to the safe, timely, and efficient development of medicines to improve patient access. It comprises of an Innovation Passport designation and a Target Development Profile and provides applicants with access to a toolkit to support all stages of the design, development, and approval process.	The criteria to obtain the Innovation Passport include innovative medicine such as ATMPs or new chemical or biological entity, or novel drug-device combination.
G-BA	**Legislative updates** New German law (GKV-FKG) approved in February 2020 gives G-BA the authority to require the collection of RWE with registry data as part of the early benefit assessment process for products with conditional approval and orphan drugs. In 2021 onasemnogene abeparvovec exceeded the €50 million sales threshold during its first six months of sales. A full benefit assessment versus appropriate comparator therapy was subsequently required, and the G-BA requested routine practice data for the product due to the lack of direct comparative data to treatment alternatives in SMA. The manufacturer was required to implement a registry study to collect the required evidence (G-BA, 2021a).	The possibility of RWE collection as part of the benefit assessment process can potentially mitigate concerns on long-term efficacy and safety for ATMPs, where this has not been adequately addressed in the pivotal trial.

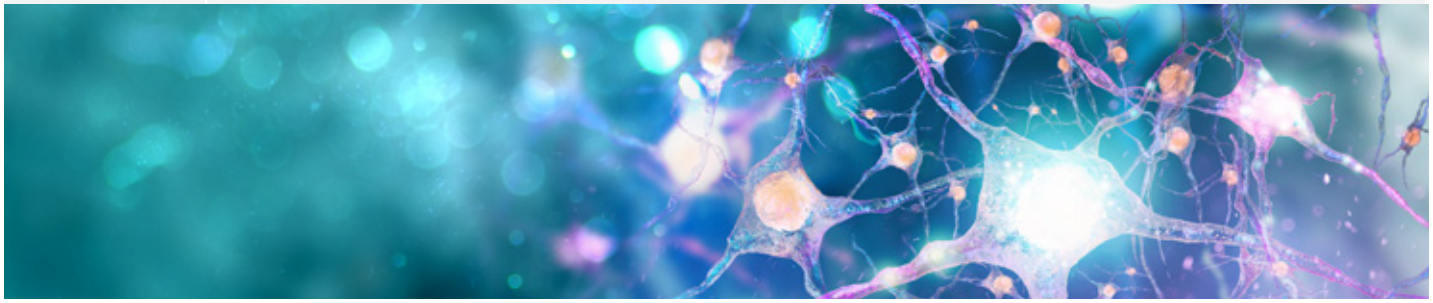
HTA agency	Recent changes	Implications for ATMPs
HAS	**New guidance for RWE** In 2021, HAS published new guidance on best practices for real-world evidence generation to support and assist the implementation of real-world studies for health products (HAS, 2021b). This came after HAS led the EUnetHTA Joint Action 3 Post-Launch Evidence Generation initiative (EUnetHTA, 2022b).	ATMP manufacturers could leverage the increasing interest in RWE and HAS's long history of using RWE and new guidance to align on potential RWE plans to complement potential data gaps.

Table 6 Key HTA initiatives across different PICOS parameters adapted for ATMPs

PICOS parameter	Key initiatives
Population	**Extrapolating the clinical effectiveness of treatment beyond the specific patient population represented in the clinical trial where more patients are expected to benefit from treatment** • The TLV has accepted pivotal trials with a limited patient population for rare diseases. For voretigene neparvovec, the trial only included patients with Leber's congenital amaurosis type 2; However, the TLV believed that the clinical results could be extrapolated to all patients with RPE65 mutation covered by the approved indication. • NICE has extrapolated the clinical benefit of onasemnogene abeparvovec beyond the trial population, which excluded infants who were older than 6 months at treatment administration. NICE anticipated that some infants aged between 7 and 12 months would benefit similarly to those 6 months and younger.
Intervention	**Staffing and infrastructure arrangements to streamline ATMP administration** • NICE acknowledged that additional training and education of staff at the specialist centres would be needed for onasemnogene abeparvovec administration, whilst health service arrangements

PICOS parameter	Key initiatives
	for treating SMA with the medicine were still in development, a NICE recommendation for reimbursement was granted as NHS England would ensure the product is directed to patients in whom the greatest clinical benefit is achieved at a reasonable cost. Additionally, the NICE committee also agreed to reimburse testing for antibodies against the adeno-associated vector serotype 9 virus capsid.
Comparator	**Accepting methods and data sources for indirect comparisons** • HTA bodies have accepted methods for indirect treatment comparisons to compare the clinical effectiveness of ATMPs investigated in single-arm trials with other treatments. HTA bodies have shown a willingness to accept greater uncertainty associated with these methods, for example, in the G-BA's benefit assessment of tisagenlecleucel. • Comparisons to natural history cohorts have also been accepted; for example, the G-BA has accepted comparisons to the natural history cohorts during the benefit assessment for atidarsagene autotemcel and also concluded a major added benefit for the pre-symptomatic subgroups.
Outcomes	**Acceptance of surrogate endpoints** • Although necessary in certain situations due to limited follow-up, as in rare or slowly progressive diseases, HTA bodies associate surrogate endpoints with uncertainty, and methodological approaches for validating surrogates are not always feasible. In France, the TC requires appraisals to be made based on clinical outcomes, although a recommendation may be made based on surrogate or intermediate endpoints. However, this will require a subsequent re-appraisal (typically in 5 years), and during this time, the manufacturer must collect RWE to substantiate the clinical benefit of the medicine. **Use of novel endpoints** • In some circumstances, novel endpoints are needed to appropriately measure the health benefits of treatment, especially for innovative therapies offering transformative improvements in clinical benefit. Voretigene neparvovec used a novel primary outcome, the multi-luminance mobility test, developed to address real-life efficacy and intended to better assess the impact of changes in contrast and luminance sensitivity. **Inclusion of vignette or Time to Trade Off (TTO) when generic HRQoL measures are not sufficient.** • Vignette-based methods may be used to derive health utilities where existing methods are unsuitable or impractical. Whilst the NICE Methods Guide states that alternatives such as vignettes are a valid alternative to EQ-5D-derived utilities, NICE appraisal committees have frequently been reluctant to accept this source of evidence. For example, in the appraisals of voretigene neparvovec and betibeglogene autotemcel, the appraisal committees were unwilling to accept these alternative sources of utilities proposed by the manufacturers. **Economic outcomes** • Inclusion of societal costs: HTA bodies may be willing to accept economic evidence beyond direct costs and are open to accepting societal costs related to working life and care outside of the healthcare system. For example, NICE has frequently considered caregiver utility values in HST appraisal process. • Lower discount rates: the NICE Methods Guide allows non-reference case discount rates if certain criteria are met. For example, NICE has considered the lower discount rates specifically for voretigene neparvovec, despite uncertainty in the clinical benefit. However, this has been applied sparingly due to uncertainty in the duration of benefits and costs.

PICOS parameter	Key initiatives
Study design	**Using biological rationale to ascertain treatment effect in the absence of long-term evidence** • In the NICE appraisal of voretigene neparvovec, the manufacturer assumed a 40-year treatment effect based on 7.5 years of follow-up data demonstrating no loss in efficacy. The appraisal committee conducted a threshold analysis to ascertain the relationship between the treatment effect duration for voretigene neparvovec and the incremental cost-effectiveness ratio. In this case, the NICE committee accepted longer-term durability even in the absence of long-term evidence. **Extrapolation of clinical benefit beyond the trial duration** • Extrapolation beyond the duration of a clinical trial is required to estimate the long-term effects of treatments, such as overall survival. Whilst there are several different types of survival models available to extrapolate data (i.e., exponential, Weibull, Gompertz, log-logistic, or log-normal parametric models), they rely on different assumptions which can produce different results with the same data. Consequently, the choice of survival model may be a cause of uncertainty, and the results of extrapolation typically require validation with external data sources, as recommended in the NICE Methods Guide. • In the NICE appraisal of tisagenlecleucel, the cure fraction varied by 35% based upon the extrapolation model used, which produced cost-effectiveness scenarios that varied between £20,046 and £44,299 per QALY. **Use of registry data to collect long-term outcomes** • The G-BA and HAS noted several limitations in extrapolating the results from the ongoing trial in benefit assessment of onasemnogen-abeparvovec, such as shorter follow-up time in pre-symptomatic patients and suggested long-term follow-up in the context of registry data to assess the effect of the medicine on mortality, morbidity, and HRQoL. • HAS highlighted that longer-term data was required to ensure the impact on overall survival and durable clinical benefit of tisagenlecleucel. HAS therefore requested to collect long-term outcomes data through the DESCAR-T register to resolve uncertainties.
Other	**Conditional recommendations, contracting, and alternative funding sources** • HTA bodies, such as NICE, have recommended conditional reimbursement routes (e.g., Cancer Drugs Fund/Innovative Medicines Fund in England), which allow ongoing data collection to address areas of uncertainty whilst providing timely patient access. • Data collection may also take place via innovative contracting methods (e.g., pay-for-performance with RWE collection, spread payments by predefined health outcomes) as part of a re-appraisal process to address uncertainty and budgetary impact challenges. **Multi-stakeholder early advice** • Early scientific advice is an established approach to identifying areas of uncertainty in a proposed clinical development plan and to define suitable approaches for evidence generation and addressing areas of uncertainty. Earlier dialogue and a pragmatic approach from the HTA perspective may lead to higher-quality evidence for ATMP appraisals with implications for access.



3.3. Future perspectives

As we prepare for the implementation of the EU HTA Regulation, we note there can be numerous benefits to be derived from EU-wide collaboration on joint assessment through harmonization of clinical data requirements and removal of duplicative assessments at the country level. This type of collaboration could improve efficiencies and reduce pressure on national HTA bodies to carry out the same clinical assessment on an increasing number of health technologies and interventions (Alliance for Regenerative Medicine, 2019). Recent changes in HTA methodologies could strengthen HTA evaluations for ATMPs and guide manufacturers to generate evidence that better meets the needs of HTA bodies.

However, there is a need to ensure that future JCAs, expected to begin in 2025 for ATMPs, are fit for purpose by considering ATMP-specific issues and ultimately ensuring these transformational therapies can be delivered to patients without delay.

Despite the observed initiatives and recent HTA method updates which consider ATMP-specific issues, ARM has identified three key challenges for ATMPs that will be crucial to address in the EU JCA:

Difficulties navigating uncertainty	Not all HTA bodies are flexible towards uncertainty arising from typical ATMP trials. While some HTA bodies have adapted their methods in specific appraisals to provide more flexibility for ATMPs or have provided a conditional recommendation based on additional evidence generation, there is still a lack of guidance on the most appropriate approach to address this uncertainty across several PICOS domains.
Lack of acceptance and harmonisation of RWE as part of the HTA appraisal and re-appraisal processes:	As highlighted in prior sections, a major source of uncertainty for ATMPs relates to the durability of their benefits in the long term. This has previously been addressed with the RWE collection. However, RWE has not yet been accepted or integrated into assessment processes by all HTA bodies. Moreover, clear, consistent guidelines on state-of-the-art and preferred methods for conducting RWE generation are not available. For EU-wide HTA, there will be a need for RWE coordination at the EU-level for a homogeneous approach to RWE collection that is relevant across Member States and appropriate in the context of a JCA.

Lack of uniformity in HTA methods across countries:	There is heterogeneity in the requirements on which different HTA bodies have based their methods. Important examples of differences include varying requirements in approach to comparisons and preferred HRQoL measures. This issue is not unique to ATMPs but can be more pronounced in rare diseases with high unmet need, which are often relevant for ATMPs.

4. Key Messages

- Despite an increasing interest in RWE, there is still a lack of harmonization between countries with no clear guidance on the most appropriate approach for collecting this evidence. Clear guidance on preferred RWE methodology should be published, following the examples by NICE and HAS.

- Guidelines on direct and indirect comparisons should provide clearer guidance on appropriate methods that could be suitable for single-arm trials, which are common for ATMPs.

- There should be continued cooperation between the EU HTA Coordination Group and ATMP developers from the time of JSC to the end of the JCA process.

The new Regulation establishes a new ecosystem across the EU (EUnetHTA, 2022a). A timeline has been put forward for different activities over the next 3 years as part of the new EU HTA Regulation, including key deadlines for ongoing EUnetHTA21 consultations on the process and methods, given that the development of methodological and transversal guidelines, templates, and procedures is the most important area of focus for EUnetHTA21.

A summary of the different topics for EUnetHTA21 consultation that are relevant to this research is provided below, together with a mapping of the relevant ARM positions.

Table 8 Timeline of events and relative importance for ARM

2022 Consultations		
Consultations relevant to this research	**Timeline**	**ARM position**
Scoping process	May 2022	In ARM's view, setting up a process mandating the selection of all requested PICOS is at risk of making the JCA inefficient and unmanageable from an operational perspective. ARM would like EUnetHTA21 to take a pragmatic approach in PICOS selection, taking case-by-case decisions based on science and input from all relevant stakeholders (as opposed to taking a unilateral approach), leading to a consensus.
Methodological guidelines on direct and indirect comparisons	May 2022	ARM understands that RCTs are the "gold standard" for HTA of conventional medicines, especially those medicines targeting larger populations and having marginal added benefit vs. standard of care. However, RCTs are not the standard clinical study vehicle for investigating the efficacy and safety of many ATMPs, which are frequently studied in single-arm trials (due to lack of feasibility of conducting an RCT or for ethical reasons). For this reason, ARM calls EUnetHTA21 to develop specific approaches for evaluating these non-RCT frameworks and addressing clinical uncertainties of ATMPs at launch, including methods for measuring uncertainty and evidence development plans for mitigating such uncertainties.
Applicability of evidence	July 2022	Encourage the use of statistical approaches for dealing with cases in which non-randomized evidence (e.g., single-arm trials, comparative observational studies, and registry data) are used to inform estimates of relative effectiveness.
Validity of clinical studies	July 2022	Single-arm studies or non-randomised evidence are often the only options for consideration for ATMPs. This evidence is deemed insufficient to estimate the relative treatment effectiveness for decision-making. Therefore, input from statisticians with specific expertise in this area should be sought for a critical assessment of the analytical approach to be used.
Comparators and comparisons	August 2022	Indirect methods are needed when there is an absence of direct head-to-head data between the intervention and comparator of interest. For ATMPs, the use of indirect comparison could be considered as common practice and necessary for evaluation, given the difficulties in conducting comparative studies due to ATMPs targeting indications with high unmet need with no labelled therapies.
Endpoints	October 2022	Guidelines need to clarify how to determine meaningful endpoints considering the unique ATMP characteristics. Also, we need to propose endpoints that are clinically relevant and suitable for assessing the outcome of the observed treatment effect in a reasonable time horizon. Define and test appropriate surrogates and their validation and demonstration of durable benefit. The Joint Scientific Consultation (JSC) process will be instrumental in agreeing on the right endpoints.

5. Recommendations

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

1 **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 rather than using it as a basis for finding 'no quantifiable benefit.'**

As observed in past national HTA appraisals, the dataset available for an ATMP at launch will not resolve all uncertainty about the treatment. There are valid scientific and medical reasons for this, including 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.

2 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. Post-launch evidence generation, such as through high-quality registries, can be valuable to address uncertainties about an ATMP that remain at launch.

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.

3 The JCA should accept single-arm studies where medically and scientifically justified and provide clear guidelines on appropriate methods and relevant sources for direct and indirect comparisons

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 needed to 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.”

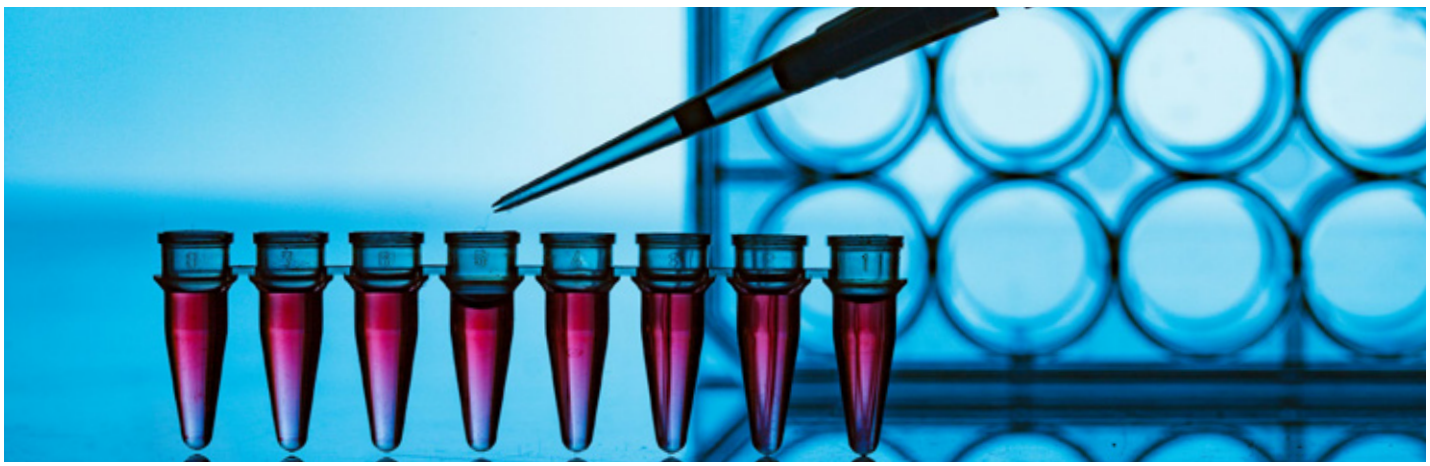
As previously mentioned, given the rarity of ATMP target diseases, the high unmet need in these conditions, and the significant clinical effect of ATMPs, it is often not appropriate or ethical to set up randomized controlled trials for these types of therapies. Therefore, ATMPs are frequently studied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

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

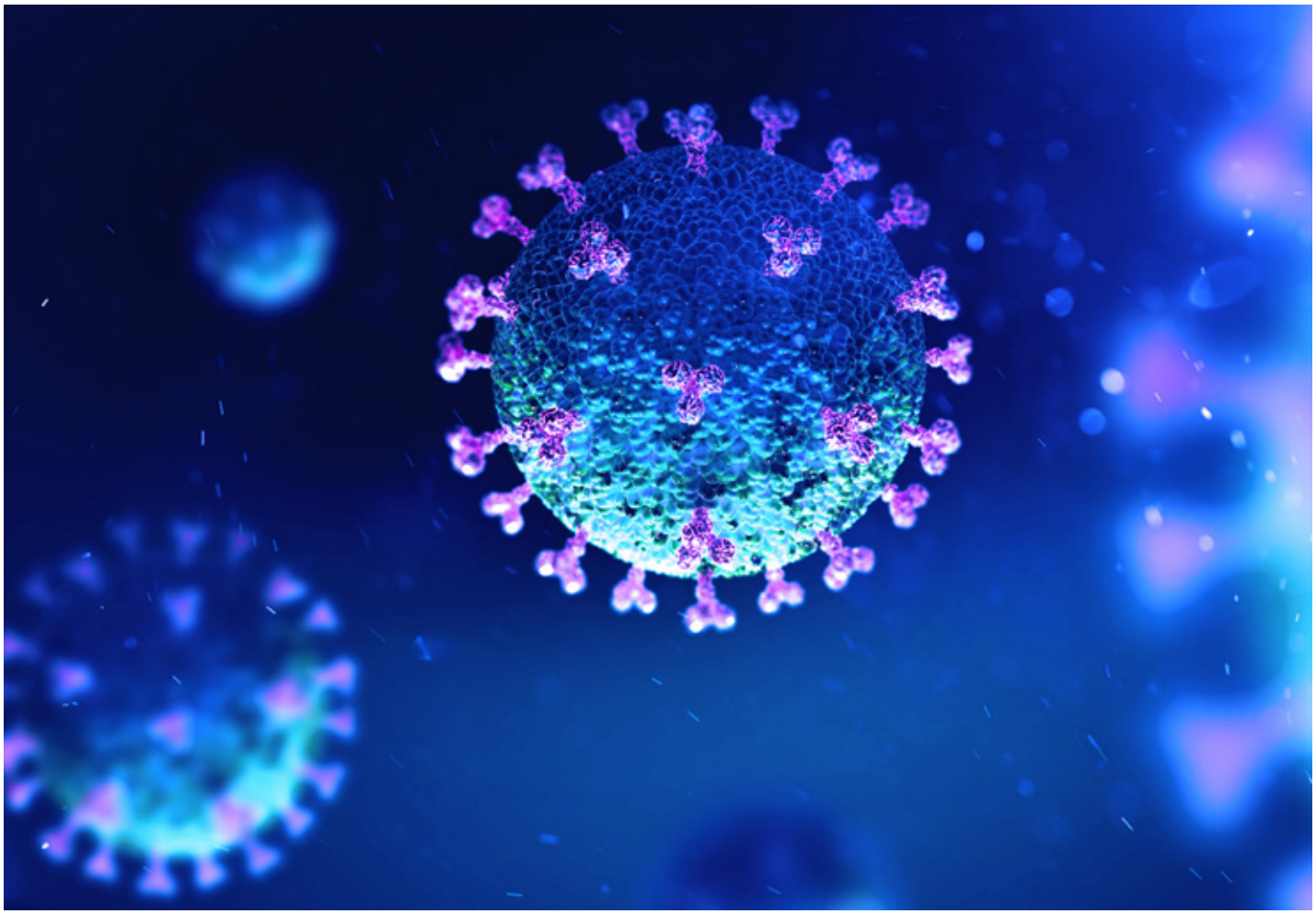
Similar to recent changes in NICE methods that allow for greater flexibility in the assessment and management of uncertainty, ARM urges the JCA agencies to accept conditional assumptions when assessing long-term treatment effect. These assumptions should be updated over time through RWE, and evidence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



5 There should be a 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.



6. List Of Abbreviations

Abbreviation	Abbreviation
ADA-SCID	Adenosine deaminase - severe combined immunodeficiency
ARM	Alliance for Regenerative Medicine
ATMP	Advanced Therapy Medicinal Product
ATU	Autorisantion Temporaire d'Utilisation
CAV	Clinical Added Value
CB	Clinical Benefit
CDF	Cancer Drug Fund
CEESP	Commission d'Evaluation Economique et de Santé Publique
CUA	Cost Utility Analysis
DLBCL	Diffuse Large B-cell Lymphoma
EQ-5D-5L	EuroQol five dimensions five levels
ERG	Evidence Review Group
EMA	European Medicines Agency
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FL3B	Follicular Lymphoma Grade 3B
G-BA	Gemeinsamer Bundesausschuss
GKV-FKG	Gesetzes für einen fairen Kassenwettbewerb in der gesetzlichen Krankenversicherung
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung
H2H	Head-to-Head
HAS	Haute Autorité de Santé
HRQoL	Health Related Quality of Life
HST	Highly specialised technologies
HTA	Health Technology Assessment
HTD	Health technology developer
ILAP	Innovative Licensing and Access Pathway
IMF	Innovative Medicine Fund
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MAIC	Matching Adjusted Indirect Comparison
MACI	Matrix-induced Autologous Chondrocyte Implantation

Abbreviation	Abbreviation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network Meta-Analysis
NRS	Non-Randomized Study
PICOS	Population, Intervention, Comparator, Outcome, and Study design
PMBCL	Primary Mediastinal Large B-Cell Lymphoma
QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
RWE	Real World Evidence
SHI	Statutory Health Insurance
SMA	Spinal Muscular Atrophy
SoC	Standard of care
TC	Commission de la Transparence
TLV	Tandvårds och läkemedelsförmånsverket
TTO	Time Trade-Off

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