Facilitating effective health technology assessment for gene therapies

Pfizer

Alliance for Regenerative Medicine

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Contributors

Lauren Diamond, Jennifer Young, Nitin Mahadev and Safiyya Gassman – *Pfizer*; Paolo Morgese - *Alliance for Regenerative Medicine (ARM)*; Amanda Whittal and Elisa Garau - *Dolon* contributed to the development of this report.

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Introduction

As of the first half of 2024, a total of 30 gene therapies, including genetically modified cell therapies, have been approved globally, with an average of five approvals per year in the past three years alone[1]. Even more gene therapies are anticipated in the coming years: there are approximately 627 ongoing clinical trials across oncology and non-oncology therapeutic areas, of which 168 are in phase two or three[2].

Gene therapies have the potential to offer value to patients and their families/care givers through long-term transformative health benefits. However, standard value assessment methods that are often designed for more conventional medicines can face a variety of challenges in accurately capturing these benefits and managing uncertainty. In order to support effective health technology assessment (HTA) for gene therapies, it is crucial to ensure HTA processes can adequately assess the specific characteristics of such novel treatments and promote patient access to those that offer promising outcomes.

There are three broad areas that cause challenges for the assessment of gene therapies within current HTA systems:

1. **Evidential uncertainty:** gene therapies currently target rare conditions and thus face the same assessment challenges as other rare disease medicines, such as small patient populations, single-arm trials, disease heterogeneity and difficulties in identifying appropriate endpoints[3]. Additionally, the potentially long-term impacts of gene therapy cannot be captured within clinical trial follow-up periods, leading to uncertainty around long-term clinical outcomes[4].

2. **Limitations of standard cost-effectiveness methods:** existing cost-effectiveness methodologies designed for conventional therapies in common conditions may be inadequate for capturing the potential long-term value of gene therapies for various reasons, including:

   - The expected cost of gene therapies is likely to exceed cost-effectiveness thresholds due to relatively high incremental costs[5] and the fact that budget impact analyses tend to be limited to one to three years, which may not reflect their potential long-term benefits[6,7]
   - Rarity of the disease is not always accounted for[8,9]
   - Cost calculations often include lifetime healthcare costs that patients would not have incurred without life-extending therapies[10], making gene therapy treatment seem less cost-effective than is true in reality.

   Moreover, globally, there is no agreed standard methodology for cost-effectiveness assessment, which results in inconsistent decision-making which can impact access to gene therapies around the world[11].

3. **Difficulties incorporating additional elements of value:** although the holistic value of gene therapies spans beyond clinical value, most HTA frameworks do not capture more comprehensive social and economic benefits, such as how the long-term potential of gene therapies can positively impact patient and caregiver quality of life, as well as their ability to return to work[6].

In this context, roundtable participants discussed areas of focus, along with opportunities and best practices, within two key domains related to facilitating effective HTA for gene therapies:

- Enhancing gene therapy evidence
- Ensuring HTA methodologies can accurately assess gene therapies based on their holistic value to patients, health systems, and society

Enhancing gene therapy evidence

Gene therapies present challenges in generating robust clinical data due to 1) the characteristics of the rare diseases they often target, and 2) the specificities of the treatments themselves.

In terms of **rare disease characteristics**, several aspects are relevant. Firstly, the limited number of patients affected by rare, genetic conditions translates into small sample sizes for clinical trials, creating a significant hurdle in generating sufficient clinical evidence[12,13]. Secondly, rare disease treatments are often assessed through single-arm trials instead of gold-standard randomized controlled trials (RCTs)[14]. This trial design can be unavoidable, as there is often no treatment comparator available for rare diseases. Moreover, it is considered unethical to withhold treatment from patients suffering from conditions with high unmet medical need and a small window of opportunity to receive a gene therapy treatment by placing them in a control or placebo trial arm. While Indirect Treatment Comparison (ITC) can be an alternative in case of lack of comparative data, its acceptance by HTA bodies remains limited or inconsistent[15]. Finally, rare diseases are inherently heterogeneous, resulting in varied responses to treatment depending on patient characteristics[16]. This reduces the generalizability and transferability of effectiveness estimates and complicates evidence interpretation[17].

In terms of **gene therapy characteristics**, the high upfront cost and long-term treatment effects from a single administration result in very specific challenges. In this case, the standard clinical trial follow-up period cannot capture the potentially long-term treatment effect, creating uncertainty regarding long-term health outcomes and cost-effectiveness[18,19,20].

The characteristics of gene therapies and the rare conditions they treat thus create uncertainties that pose difficulties for current HTA systems, which are more tailored for assessing treatments for chronic diseases, for example. Roundtable participants, therefore, noted the need to enhance gene therapy evidence to facilitate effective assessments and patient access. To achieve this, they highlighted several promising opportunities, drawing on examples from established best practices.

Natural history studies can address clinical evidence challenges

A natural history study is a preplanned observational study that aims to track disease progression[21]. This type of study helps to identify factors, including genetics or treatments, associated with disease development or outcomes[21]. Therefore, natural history studies are crucial for understanding disease etiology, pathophysiology, and health outcomes achieved with standard-of-care treatments[21]. These studies have several practical applications:

- They can be helpful when developing and validating trial endpoints, including surrogate endpoints, especially for rare diseases with a lack of well-validated outcome measures[22].
- Pooling data from natural history studies (e.g., rate, patterns of and time to progression, levels of specific biomarkers, etc.) can help provide a better understanding of a disease and treatment effects, and reduce evidential uncertainty[23]. As highlighted in the roundtable, if there are high levels of disease heterogeneity, this type of study can help identify comparators for different disease groups based on specific disease progression and clinical manifestations.
- The data can help populate health economic models used in HTA submissions and serve as a historical control or indirect external comparator in single-arm studies[24,25].

Real-world data (RWD) can serve as a source for natural history studies, especially when RCTs may not be feasible[23]. For example, a review of 433 single-arm trials based on HTA submissions in 21 countries highlighted that the acceptance rate of single-arm trials increased from 48% to 59% with the inclusion of an external control based on RWD[26]. In line with these findings, an IQVIA analysis of 16,515 HTA reports from 83 HTA bodies

across 33 countries reveals that the inclusion of Real-World Evidence (RWE), generated using RWD, in submissions has significantly increased, rising from 6% in 2011 to 39% in 2021[27].

Still, there are varying degrees of RWD acceptance and use in HTA. A review of external controls in HTA submissions in France, Germany and the United Kingdom (UK) between 2015 and 2021 highlighted that HTA in the UK more often considered RWD in their decisions, compared to France and Germany[28].

At the European Union (EU) level, advanced therapy medicinal products (ATMPs), including gene therapies, will undergo a new EU-wide Joint Clinical Assessment (JCA) as of 2025[29]. This assessment aims to harmonize clinical data requirements and remove the need for multiple HTAs at the country level. The JCA may also provide the opportunity to utilize RWD more consistently and address difficulties in generating evidence for ATMPs. Recent initiatives taking place ahead of the JCA implementation seem to highlight this possibility. A multistakeholder workshop organized by the HTA Secretariat and stakeholders involved in the JCA process, such as patient associations, health professionals and other experts, emphasized the importance of a sound approach to evidence (e.g., single-arm trials, registry data and RWD) and the need to identify best practices[30].

Best practices could inform more consistent use of RWD and natural history studies to support gene therapy evidence generation. Several existing examples can pave the way for future products.

Best practices

The Duchenne Natural History Study (DNHS), driven by the Cooperative International Neuromuscular Research Group (CINRG), is the largest prospective natural history study for Duchene Muscular Dystrophy (DMD) to date. It recruited 440 patients from 20 centers in nine different countries and followed up with them for up to 10 years[31]. This study was used as an indirect comparison in the HTA submission of Translarna in the UK. Based on the comparison, the National Institute for Health and Care Excellence (NICE) stated that uncertainty remained, but acknowledged that the drug could slow disease progression[32].

In the UK HTA of a therapy for a rare form of non-Hodgkin lymphoma (NHL), comparator data came from a European chart review – a retrospective observational study collecting natural history data over 10 years. The manufacturer created a matched cohort by selecting a subset of patients in the European chart review with characteristics similar to those of the patients in their trial[33,34]. Although the therapy exceeded the cost-effectiveness threshold and was not reimbursed, the HTA assessors accepted the comparator data. They noted that while there was still uncertainty around clinical effectiveness, the treatment appeared to be more effective than existing therapeutic options based on the indirect comparison combined with expert and patient opinion.

While improving RWD collection is essential for evaluating gene therapies, this alone may not fully address the challenge of differing approaches among HTA bodies. Each body evaluates new treatments based on distinct criteria, which can create assessment inconsistencies. This highlights the need to strengthen evidence generation to meet the requirements of HTA bodies and align these efforts with mechanisms that ensure timely patient access to innovative medicines.

Patient-reported outcomes can bolster evidence generation

When there is evidential uncertainty, clinical endpoints can be supplemented by patient-reported outcomes (PROs), a report of a patient's health condition derived directly from the patient[35]. PROs enable patients to convey their experience during and after treatment. They provide insights into treatment effects that may not be captured by clinical endpoints but can help inform HTA decisions. PROs can capture, for example, any toxicities experienced and the overall impact on health-related quality of life (HRQoL) or symptoms[36]. Beyond physical elements, PROs can also capture shifts in mindset, an aspect particularly relevant for gene therapy[36]. Indeed, the potential long-term benefit of these products can alleviate the psychological burden and reduce constant preoccupation with the disease[36]. Therefore, incorporating routine PRO collection in registries can provide additional data to assess the benefit and risk profiles of gene therapies at follow-up intervals that would not be feasible in a clinical setting[37].

Best practices

WFH
WORLD FEDERATION OF HEMOPHILIA

The World Federation of Hemophilia (WFH) gene therapy registry is a prospective and observational registry documenting the outcomes of hemophilia patients treated with gene therapy. The core data set includes information on demographics, clinical history, infusion details, safety, efficacy and PROs. PROs are collected through a patient mobile application in which patients are asked to answer a short series of questions every six months, and to complete various questionnaires on a regular basis[38]:

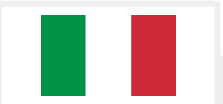
- *The Patient-Reported Outcomes Burdens and Experiences (PROBE) multinational questionnaire aims to collect insights about the impact of hemophilia on daily life through questions on lifestyle, quality of life (QoL) and health concerns[39].*
- *The coreHEM Mental Health Outlook questionnaire (coreHEM-MHO) is a tool specifically developed to evaluate the mental health of individuals receiving gene therapy or other durable hemophilia treatments[40].*

Hunter Outcome Survey

The Hunter Outcomes Survey (HOS) is a registry that collects a variety of data, including PROs, through the Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS)[40]. The HS-FOCUS includes questions on the patient's daily life, well-being, satisfaction with treatment, hospitalizations and QoL[41].

PROs are used in various ways within the HTA process to inform decision-making[42]. For example, an analysis of HTA reports from Belgium, England, France, Germany, Italy, Netherlands, Norway, Scotland, Sweden, and the USA for two gene therapies, approved by the Food and Drug Administration (FDA) in 2017 and 2019 respectively, highlighted the various ways PROs from patients and carers are taken into account[42] .

Despite their relevance, assessing and validating PRO measures that can both accurately capture disease-specific characteristics and be acceptable for HTA bodies is often difficult[43]. It is, therefore, essential to improve the development and use of PRO measures to ensure they can be routinely collected to effectively aid decision-making.



The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated PRO used to measure HRQoL in cystic fibrosis[44]. The advantage of this PRO is the ability to effectively capture changes in lung function and HRQoL compared to generic instruments[44]. Improvements in HRQoL resulting from this PRO have contributed to the positive HTA outcome and subsequent inclusion of an orphan drug in Italy's list of innovative drugs[45,46].

Global registries can enhance gene therapy evidence

Global registries can enhance gene therapy evidence in several ways. First, they enable the pooling of data across diverse geographies, which helps to overcome the lack of natural history data available for and low frequency/numbers of patients with a particular rare disease. They also allow RWD collection and monitoring of long-term safety and treatment outcomes of gene therapy. This can address the uncertainty around long-term impact and inform HTA decisions. Furthermore, global data collection efforts can promote international collaboration and facilitate the sharing of best practices and expertise at a broader scale.

Developing global registries does, however, require long-term investment in data collection infrastructure and a clear framework to ensure the generation of agreed and consistent robust data. This commitment can be facilitated by strong collaboration amongst stakeholders, including patient organizations, scientific societies and industry, as illustrated by the examples below.

Best practices

SMARTCARE

SMArtCARE is a prospective, multinational registry supported by industry but managed by the SMArtCARE network of clinicians and patient organizations that gathers longitudinal data from existing spinal muscular atrophy (SMA) registries[47]. In 2023, the registry provided a manufacturer with aggregated, anonymized data on children with SMA type two treated with their product. This data was included in the HTA assessment for expanding reimbursement in Italy[48].

TREAT-NMD Neuromuscular Network

The TREAT-NMD Global Registry Network brings together 64 independent neuromuscular disorders (NMD) registry members, who together collect data on a total of ~80,000 patients. The collaboration increases the scale of the data collection, promotes the sharing of learnings across registries and creates efficiencies where possible (e.g., through centralized contracting)[49].

At the same time, some countries are also moving toward localized data collection. For example, under the German Law for More Safety in the Supply of Medicines (GSAV), the Federal Joint Committee (G-BA) can require pharmaceutical companies to collect real-world data for certain drugs, including orphan medicines and gene therapies[50]. In this case, the product is immediately available for patients and the collected data informs benefit re-assessment[51]. As of now, data

collection has begun for gene therapies targeting hemophilia and spinal muscular atrophy[52].

Although local efforts are promising, there is an opportunity to better align them with global and regional data collection initiatives. Without this coordination, there is a risk of duplication, inefficiencies, and fragmented data that could ultimately hinder broader patient access.

Manufacturers can highlight the steps they are taking to address uncertainties

At the time of HTA submission, there is often a high degree of uncertainty related to trial design and trial duration, which cannot fully capture the long-term impact of gene therapies. This was captured in a recent analysis of 46 HTA reports for nine cell and gene therapy products in Canada, France, Germany, Italy and the UK, in which uncertainty was considered relevant in 87% of the reports[4].

Another study investigating gene therapy HTA reports from the Netherlands, UK, and Scotland indicated that HTA bodies show greater acceptance of these uncertainties if manufacturers show that they are taking concrete steps to address them[53]. This communication instills confidence that although uncertainty exists, there is a proactive and committed approach to managing it. Furthermore, it demonstrates transparency and accountability by providing a clear picture of the ongoing efforts to enhance gene therapy evidence.

Some HTA bodies have published guidance on their expectations for real-world evidence (RWE) collection and use, which manufacturers can utilize to outline their plans for managing gene therapy uncertainties.

Best practices

NICE
National Institute for Health and Care Excellence

NICE's RWE framework offers comprehensive guidance on generating and utilizing RWE. The framework details NICE's expectations for planning, executing, and reporting RWE studies. The framework also provides recommendations for implementing non-randomized studies, such as observational studies or clinical trials utilizing RWE, to establish an external control[54].

In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) guidance for reporting RWE provides information on what regulatory bodies and HTA agencies should expect when evaluating studies incorporating this type of evidence[55]. The guidance also provides specific recommendations on high-quality RWE studies and clear and transparent reporting, covering aspects like study design, data collection methods, and appropriate statistical analysis[55]. A recommendations checklist serves as a tool to ensure that submissions adhere to the guidelines outlined in the document[55].

Nevertheless, manufacturers' proactivity in addressing evidence gaps may not fully address the broader issue that HTA bodies often assign a low value to innovative therapies due to evidential uncertainty, for example, the lack of long-term efficacy data. Without this data, HTA frameworks struggle to assess long-term benefits, potentially delaying or denying patient access. Clear communication and proactive steps from manufacturers help, but the friction caused by uncertainty remains a significant barrier in the HTA process that needs to be addressed.

Ensuring HTA methodologies can accurately assess gene therapies based on their holistic value to patients, health systems, and society

The specific characteristics of gene therapies and the rare diseases they currently treat create challenges within conventional HTA standards. There are several reasons for this, including:

1. Their high value may exceed that of many other interventions (e.g., considering the severity of the diseases they often treat or the potential step change in length and quality of life they may offer[4])

2. The possible long-term effects of gene therapies and the inability of short-term trials to provide sufficient certainty around these effects[6,7]

3. As novel 'disruptive technologies,' they require an assessment framework that can more accurately capture broader elements of value.

Regarding the latter aspect, broader elements of value are important to consider for a comprehensive assessment[6], but current HTA and pricing and reimbursement processes focus predominantly on clinical and cost-effectiveness. This focus can overlook other elements of value, such as disease severity and the impact of treatment on family/caregivers or society [56]. While disease-related value elements are accounted for by some HTA bodies in their evaluations (e.g., disease severity, unmet need) broader elements such as the value of long-term benefits or societal impacts are rarely considered[4,57]. For example, in the UK, NICE incorporates a disease-severity modifier in decision-making, which allows consideration of the severity of the disease and the extent of unmet medical need when calculating Quality-Adjusted Life Years (QALYs)[58]. On the other hand, in an analysis of 46 HTA reports for ninecell and gene therapy products in Canada, France, Germany, Italy and the UK, value to caregivers was considered in only 30% of the reports, while severity was considered in 76%[4].

The wider implementation of broader value elements in HTA frameworks can be challenging due to the variability in how different HTA bodies assess and capture them, and the lack of alignment on how they can be consistently applied across different treatments[59]. This variability makes it difficult for a single clinical study to deliver all variables that would be required to meet the needs of multiple HTA bodies.

The necessity for a broader notion of value for gene therapies and the uncertainty around their long-term impact point to a need to ensure existing assessment systems are revised as necessary to ensure they are fit for purpose for novel therapies.

Based on these considerations, a promising opportunity to improve gene therapy HTA were discussed, drawing on examples from established best practices.

Flexibility and adaptations within HTA frameworks could help better recognize the value of gene therapies

Current assessment frameworks were primarily developed for more prevalent diseases and may not accurately capture the full value of gene therapies[60]. There is thus an opportunity to make adjustments within existing HTA systems to better capture the specific characteristics of gene therapies.

Several countries have made efforts to create *flexibility* in assessment frameworks for the treatment of rare and severe diseases with high unmet need. In the UK, for instance, a cost-effectiveness threshold of £100,000 per QALY for ultra-rare diseases is applied vs the standard £20-30,000[61]. In Italy, drugs can be classified as "innovative" based on therapeutic need, added therapeutic value, and quality of evidence, granting them dedicated funds and immediate market access[62].

At the European level, the JCA for ATMPs, including gene therapies, will start in 2025[29]. While concerns remain around the application of the JCA in practice and how the evidence will be evaluated compared to standard treatments for wider populations, there is an opportunity to ensure streamlined processes are tailored appropriately for gene and cell therapies.

Given the novel and potentially transformative quality of gene therapies, significant discussion has focused on the need to ensure HTA frameworks are appropriately calibrated to recognize their unique characteristics. Some countries have made strides towards this.

Best practices

Since January 2020, Canada has implemented a distinct assessment process for gene and cell therapies[63]. This includes elements from both the evaluation process for medicines and medical devices, such as ethical and implementation considerations[63]. This review process was implemented based on learnings from assessing the first two chimeric antigen receptor (CAR) T-cell therapies[64].

HAS
HAUTE AUTORITÉ DE SANTÉ

In 2023, the Haute Autorité de santé (HAS) in France published a new HTA methodology reflecting greater acceptance of uncertainty for promising therapies[29,65,66]. HAS outlines key considerations for manufacturers submitting dossiers based on uncontrolled trials and is open to high-quality indirect comparison data or data from control groups. However, the use of this data must be justified in advance, including the rationale for the lack of randomization.

In addition to creating flexibility within current HTA frameworks, adaptations to include additional elements of value would allow for a more comprehensive assessment of the impact of gene therapies. The inclusion of such elements of value can:

- Provide insights into the therapy's broader societal impact (e.g., effect on patients and caregivers), thus reflecting its full value.
- Consider the therapy's wider economic impact beyond direct healthcare costs to more accurately evaluate it in economic models.

Currently, willingness to accept additional value elements differs across HTA bodies. An analysis of five drugs assessed by 15 HTA bodies highlighted the importance of including these broader value elements – adding caregiver's HRQoL, for instance, increased QALYs in 19 out of 23 analyses[67]. At the same time, inconsistency is generally found in the inclusion of additional value elements[4], leaving an opportunity for adaptation to HTA processes that do not yet include them.

Some HTA bodies have included or are considering the inclusion of additional elements of value in the evaluation of cell and gene therapies, as outlined below.

Best practices

In the Netherlands, the HTA of a gene therapy included carer HRQoL in a scenario analysis[68]. In January 2024, new guidelines for conducting economic evaluations in healthcare were published[69]. According to the guidelines, costs incurred by patients and their families, such as those associated with informal care should be included in the economic evaluations. Additionally, when relevant to the intervention, the quality of life of informal caregivers should also be considered and incorporated into a scenario analysis.

The Dental and Pharmaceutical Benefits Agency (TLV, Sweden) acknowledged there are reasons to consider HRQoL for caregivers, particularly in cases where the disease significantly impacts their lives and a gene or cell therapy can improve their QoL. At the same time, TLV acknowledged that including caregiver HRQoL may lead to uncertainty and should be carefully managed. For this reason, TLV is still working to refine when and how such elements of value should be included[6,70].

The Valuation of Lost Productivity (VOLP) questionnaire was used to measure work productivity loss and costs, including absenteeism and presenteeism in Canadian patients with multiple sclerosis (MS)[71]. Furthermore, the questionnaire was implemented to measure productivity loss, caregiver burden and other costs in the evaluation of whole exome sequencing (WES) in children with suspected genetic disorders[70].

Every opportunity to ensure effective HTA for gene therapies requires active patient involvement

The opportunities that emerged from the roundtable discussions highlight that there can be a sustainable future for gene therapies with collaborative efforts. However, it is critical to note that all of the efforts and the opportunities discussed require patient involvement.

When it comes to data collection, it is crucial to include patients / caregivers / patient organizations early and throughout to ensure design and outcome measures are appropriate and fit for purpose. There is an opportunity for patients to be substantially involved; an analysis of 37 registries worldwide revealed that although 57% included PROs, only 38% involved patients in the registry design[72]. Early patient involvement can promote a commitment to data generation, ensure patient data belongs to the patient and facilitate the collection of extensive and relevant data[73].

Patient involvement can also ensure that endpoints are meaningful to the patient and data collection is not an excessive burden, which is essential for effective data collection. For example, in the case of the Expanding Communications on Hemophilia A (ECHO) registry, data collection was planned for five years, but the registry was closed after just two years[74]. This was attributed to several challenges, including the burden for patients and investigators of multiple PRO measures and insufficient patient engagement.

Greater patient engagement can also improve access to innovative treatments by generating evidence that supports manufacturers' HTA submissions. For example, Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis) is a multinational project established by Duchenne UK to develop tools and evidence that can support the HTA of new DMD medicines. The project involves patient organizations, clinicians, pharmaceutical companies and HTA bodies[74]. It has led to the development of several types of evidence, including a natural history model, a DMD-specific HRQoL measure, and an economic model that pharmaceutical companies can apply for new treatments[75].

The gap between conventional HTA and gene therapy-ready assessment processes is slowly closing in some countries. Continuing this trend can enable more accurate assessments of gene therapy benefits and uncertainties, and support the uptake of promising gene therapies for rare diseases and beyond.

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