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EXPERT ROUNDTABLE

Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose?

CONSULTING | REPORT
JUNE 2022

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Please cite this report as:
Besley, S., Henderson, N., Towse, A. and Cole, A., 2022. Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose? OHE Consulting Report, London: Office of Health Economics. Available at: www.ohe.org/publications/health-technology-assessment-gene-therapies-are-our-methods-fit-purpose

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Funding

This consulting report was commissioned and funded by Pfizer, who maintained oversight of the project and had the opportunity to review and provide feedback on the content. However, any views expressed in this report belong solely to the authors and do not reflect the views, thoughts, or opinions of Pfizer.

Acknowledgements

Insights were gathered from a group of international experts, who contributed their time and expertise to the key themes and solutions described in this report. While the content of the final report is the sole responsibility of the report's authors, we would like to thank all the individual experts for their unique and insightful contributions to the content: Isabelle Durand-Zaleski, Mike Drummond, Ulf Persson, Wolfgang Greiner, Renske ten Ham, Americo Cicchetti and others who would prefer to remain anonymous. It should be noted that individuals' participation in the expert panel was as subject experts rather than representatives of their respective organisations.

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Executive Summary

Gene therapies represent a new era of medicine, offering the potential for truly transformational health gains, and further benefits for society and health systems. Gene therapy is particularly relevant to rare disease patients, as more than 80 per cent of rare diseases have a known monogenic (single gene) cause. In contrast to traditional small molecule medicines, gene therapies have the potential to correct underlying genetic defects, offering the potential for transformational health gains rather than simply managing symptoms. Moreover, successful gene therapy may require only a single dose to confer lifelong improvement rather than requiring a lifetime of ongoing treatment, thereby dramatically reducing costs associated with years of chronic care management.

Given the potential long-term nature of the health gains associated with gene therapies, there is often substantial uncertainty in outcomes which complicates the use of conventional health technology assessment (HTA) approaches. Furthermore, current HTA methods may not fully capture the potential broader value of gene therapies, such as decreased burden on the patient resulting from potentially one-time or short treatment regimen, value of hope and spillover effects on carers and family. There are also concerns about budget impact and healthcare systems' financial sustainability. As a result, it has been recognised that current HTA methods and evidence generation activities need to evolve in order to fully realise the potential of gene therapies and facilitate patient access. This report uses a mixed-methods approach to review and build on the appropriate path forward.

Our recommendations are informed by a targeted literature review and the insights of an international panel of HTA and health economics experts. We circulated the findings of the literature review and a pre-meeting survey with the experts to gather opinions and observations on the assessment of gene therapies in general and in their countries of expertise. We then hosted a roundtable to discuss key areas of disagreement and to work towards building consensus on actionable recommendations.

RECOMMENDATIONS TO BETTER CAPTURE THE VALUE OF GENE THERAPIES:

1. Incorporate methods to recognise the potential lifetime benefits of gene therapies by including a lifetime perspective in modelling accompanied by sensitivity analysis including of the discount rate.
2. Operationalise additional elements of value as part of the decision-making process within HTA, on the basis of continued research.

RECOMMENDATIONS TO ADDRESS UNCERTAINTY IN OUTCOMES:

3. Develop transparent standards for the inclusion of RWE and surrogate endpoints in HTA.
4. Include outcomes-based arrangements or other value-based arrangements as part of or following HTA to mitigate uncertainty in long term outcomes whilst enabling patient access.
5. Expand data collection through registries and international collaboration.
6. Enable early multi-stakeholder dialogue, including patient representatives, to align on feasible and appropriate HTA evidence packages.

Many of the challenges associated with the evaluation of gene therapies are not unique to these technologies, but it is well recognised that they face a high concentration of these challenges. Therefore, to unlock the potentially transformational promise of gene therapy for patients and society, overcoming them should be considered a priority. The recommendations provided in this report demonstrate the practical HTA tools available to work toward this goal.

1. Introduction

Gene therapies may transform lives. By modifying or manipulating gene expression, gene therapies alter the biological properties of cells allowing for the root cause of a disease to be targeted and thereby resulting in the potential to halt or change disease progression (FDA, 2020; Firth et al., 2021). This means that, in contrast to treatments of chronic conditions, these therapies are currently offered as one time or short-duration treatment regimens, associated with potentially long-term benefits (Firth et al., 2021). These benefits may include eliminating or reducing the need for chronic treatments to manage disease symptoms, which may also be associated with reductions or eliminations in the costs associated with chronic care.

Gene therapy is particularly relevant to rare disease patients: approximately 80% of rare diseases have been identified as having genetic origins (NIH, 2017; Eurordis, 2022). Whilst these diseases are extremely diverse in terms of the age at which symptoms occur and the severity and nature of these symptoms, they are often life-threatening or chronically debilitating. The development of these treatments presents a new combination of challenges, and a number of the factors driving their benefits to patients and society are of a different nature to those arising from more conventional treatments. To create an enabling environment for the development of gene therapies and ultimately the treatment of rare disease patients, these unusual factors must be taken into account in reimbursement decisions. In particular, appropriate processes and methods for health technology assessment (HTA) are crucial to ensure that the breadth and magnitude of potential benefits are captured, and this may require some modifications to the current assessment pathways available (Marsden and Towse, 2017; ten Ham et al., 2020) or new pathways entirely. Many of the HTA challenges faced by gene therapies are not unique to these technologies. Conventional (i.e., non-gene) treatments for small populations can and do also face the same barriers. However, the challenge for gene therapies is that they are likely to face a higher concentration of these problems (Marsden and Towse, 2017).

A summary of the HTA outcomes for a selection of gene therapies can be observed in Table 1. There is a considerable degree of variability in HTA decision outcomes both within and between countries, suggesting current inequity in patient access. Although variation in access to treatments is not uncommon, evidence provided by Tunis et al. (2021) suggests that in a sample of the health plans in the US, 67% of cell and gene therapies have restrictions compared with 30% for other orphan medicines. While we are not aware of similar analyses completed in other contexts, this evidence suggests that gene therapies may be subject to more restrictions and high variability in access compared with other treatment types.

TABLE 1: OUTCOMES FROM THE HTA OF GENE THERAPIES

Name	France	Germany	UK	Italy	Spain	Sweden	Canada	Netherlands
Talimogene Laherparepvec (Imlygic®)	Not assessed	No added benefit	Recommended with restriction	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (Strimvelis®)	Not assessed	No added benefit	Recommended	Recommended (List H)	Not reimbursed	Not assessed	Not assessed	Not assessed
Tisagenlecleucel (Kymriah®)	Recommended (for both indications)	Non-quantifiable added benefit (for both indications)	Funded via CDF with CED scheme (for both indications)	Reimbursement with restriction	Payment at result (for both indications)	*Recommended with restriction for ALL *Not Recommended for DLBCL	Recommended (with price reduction)	Recommended with restriction for ALL Not recommended for DLBCL
Axicabtagene ciloleucel (Yescarta®)	Recommended	Non-quantifiable added benefit	Funded via CDF with CED scheme	Reimbursement with restriction	Payment at result	*Reimbursement with restriction	Not assessed	Recommended
Voretigene neparvovec (Luxturna®)	Recommended	Considerable added benefit	Recommended (HST)	Reimbursement with restriction	Ongoing	*Recommended	Recommended (with price reduction)	Recommended with restriction
Betibeglogene autotemcel (Zynteglo®)	Recommended with restriction	Non-quantifiable added benefit	Ongoing/Suspended	Not reimbursed	Ongoing	*Assessed by Nordic collaboration FINOSE, No recommendation	Not assessed	Recommended with restriction
Onasemnogene abeparvovec (Zolgensma®)	Recommended with restriction	Ongoing (Mandated collection of RWE due to limited clinical data)	Recommended with restriction (HST)	Reimbursement with restriction	Ongoing	*Reimbursement with restriction	Recommended (with restriction and price reduction)	Recommended with restriction (joint price negotiation with Belgium & Ireland)

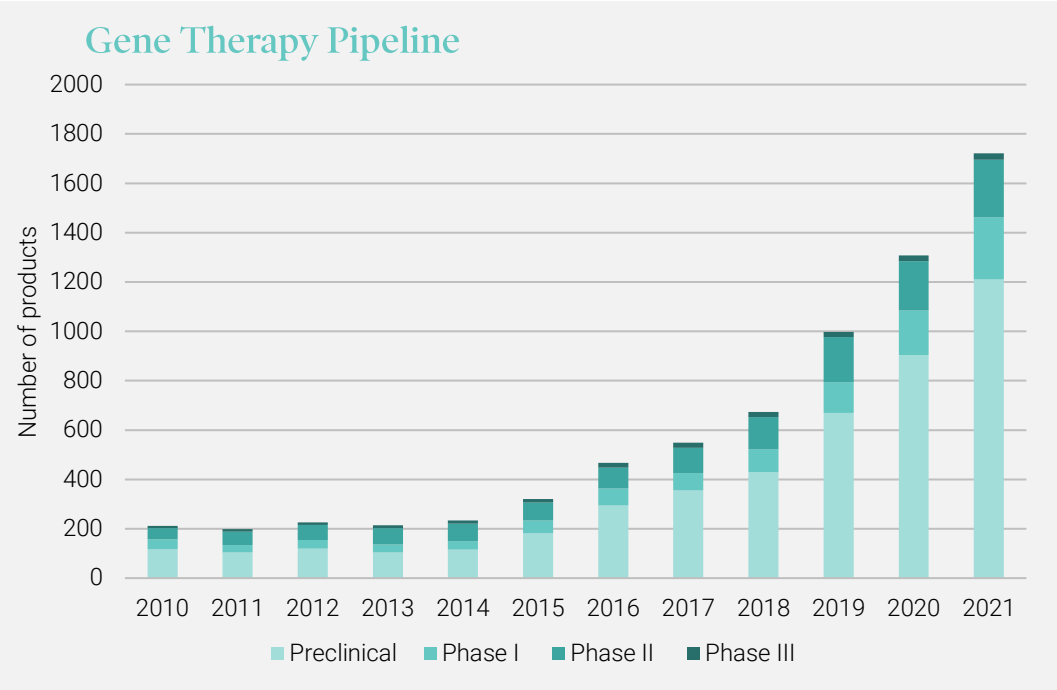
ATU: Autorisation Temporaire d'Utilisation (Temporary Authorisation for use), CDF: Cancer Drugs Fund, CED: Coverage with Evidence Development, CNN: not yet assessed, H list: Hospital only, HST: Highly Specialised Technology, RWE: Real world evidence, ALL: B-cell acute lymphoblastic leukaemia, DLBCL: Diffuse large B-cell lymphoma.

*Product was assessed by TLV in Sweden. TLV concluded that benefits are associated to high uncertainty and follow-up should be carried out continuously. TLV advice was be considered by the NT council for decision making.

The current high variability in patient access to gene therapies may be a result of the numerous challenges encountered in their HTA, and diversity in approach between countries in dealing with them. Solutions should be found to tackle these issues and deal with them in a more consistent manner, as HTA bodies will be tasked with assessing a growing number of these innovative therapies in years to come. The number of gene therapies in the pipeline has continued to rise rapidly in recent years, as seen in Figure 1. In 2021, there was over 8 times the number of gene therapies in the pipeline compared with 2010. Potential upcoming gene therapies target many therapy areas, but mainly oncology, rare diseases, and alimentary/metabolic disorders. This demonstrates the vast potential opportunities associated with gene therapies and shows that HTA of gene therapies will continue to be required. Therefore, it is imperative that HTA and surrounding processes evolve to identify and enable those opportunities to be assessed in a way that provides access for patients and value for health systems. This report explains why change is needed to be able to effectively assess gene therapies and provides recommendations for how the challenges presented during HTA should be overcome.

As noted above, the challenges are not unique to gene therapies. Therefore, it is important to recognise that the recommendations suggested in this report should be applied consistently across HTA of other technologies where similar issues arise. However, given the characteristics of gene therapies and concentration of issues arising, the impact of those recommendations may be more significant for gene therapies compared with other technologies.

FIGURE 1: GENE THERAPY PIPELINE BY CLINICAL TRIAL PHASE.



SOURCE: OHE ANALYSIS OF PHARMAPROJECTS DATA

1.2 Methods

We adopted a mixed-method approach combining desk research and a two-phase interaction with an international panel of experts.

We undertook a literature review identifying the key challenges currently associated with conducting HTA of gene therapies, as well as possible solutions. The literature review was pragmatic rather than systematic, using PubMed and Google Scholar and was restricted primarily to the past five years (2017 onwards) using the following search terms "HTA", "Health technology assessment", "gene therapy", "gene therapies", "regenerative medicine", "GTx" "Advanced Therapy Medicinal Products" "ATMP". Published, unpublished and grey literature were all reviewed.

This desk research was supplemented by eliciting expert opinions from a panel of eight international experts covering eight countries (Italy, France, UK, Spain, the Netherlands, Sweden, Germany and Canada). Our experts are academics in the field of HTA and health economics with methodological expertise in the HTA of gene therapies. We interacted with experts through two main phases of engagement, undertaken between March and April 2022:

1. Background paper & pre-meeting survey – a background paper summarizing the key challenges and solutions offered by the literature to date was shared with experts alongside a pre-meeting survey, where we obtained feedback from each individual on the issues and their relative priority, how they manifest in practice and the potential solutions.

2. Virtual Roundtable – during a four-hour virtual roundtable, we discussed the challenges of HTA of gene therapies according to four key themes, playing back the results of the pre-meeting survey in order to highlight key areas of convergence or divergence of opinion. The discussion focused around trying to establish consensus on the challenges and solutions, thereby building a set of recommendations and next steps for the future of HTA for gene therapies.

1.3 This report

A summary of the literature is presented in section 2, annotated with the expert panel's further reflections on the challenges and potential solutions. In section 3, we provide a brief description of how some of the challenges have presented and been dealt with in practice, including a deeper dive into an example of a recently assessed gene therapy for children with spinal muscular atrophy (SMA): onasemnogene abeparvovec (Zolgensma®). In section 4, we bring together the insights collected to provide key recommendations, representing priorities for change in HTA methodology to better realise the potential of gene therapies.

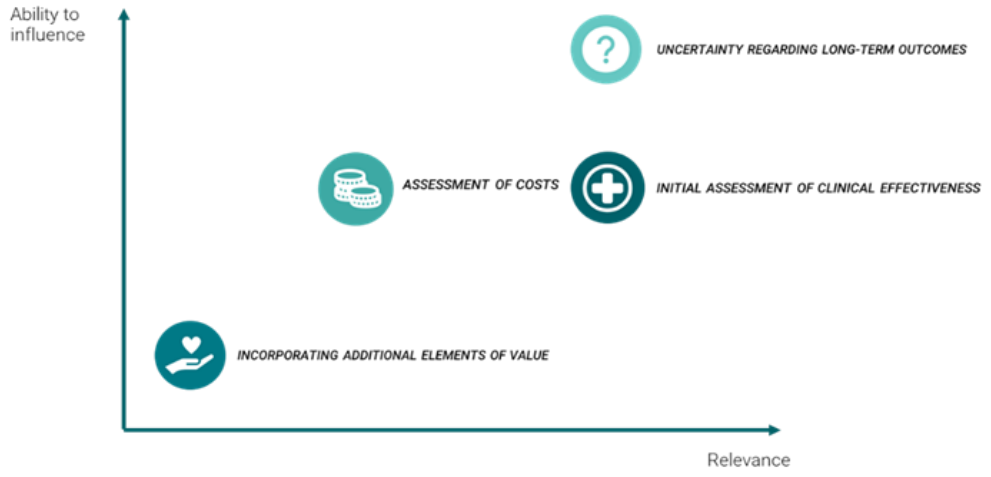
2. What are the current challenges and opportunities for improvement in the HTA of gene therapies?

The innovative nature of gene therapies and the way they can benefit patients requires innovation in the way they are assessed and approved. Without this, there is a real risk that the potentially transformative nature of these therapies is not recognised during HTA, resulting in the benefits of gene therapies not being realised by patients and society. In order to progress and agree on what "innovation" in HTA methods should look like, it is necessary to first understand the rationale for why change is needed.

In this section, we outline the main limitations in current HTA methods as applied to gene therapies and the resulting challenges this leads to in their assessment and approval. From our analysis of the literature, we group the issues into four main themes: (1) initial assessment of clinical effectiveness, (2) uncertainty regarding long-term outcomes, (3) incorporating additional elements of value and (4) assessment of costs. Within each theme, we first set out the challenges and present potential solutions from the literature. We then provide additional insights gained from our expert panel, supplementing the solutions proposed in the literature with additional solutions discussed during the roundtable by our expert panel. These insights are presented in orange textboxes. A full summary of challenges and potential opportunities for improvements is provided at the end of the section in Table 2.

The expert panel provided initial feedback on the challenges and proposed solutions through a pre-meeting survey. Figure 2 shows their relative prioritization of the challenge themes according to (a) how relevant they are to the HTA of gene therapies and (b) the ability for the challenges to be addressed by changes in HTA methods or processes. It shows that our expert panel viewed uncertainty regarding long-term outcomes is a critical area of concern, while also being an area in which change is achievable in the short term to medium term. The initial assessment of clinical effectiveness is viewed by our panel as being equally relevant but more challenging to overcome.

FIGURE 2: PRIORITISATION OF THE CHALLENGE THEMES BASED ON THE PRE-MEETING SURVEY RESULTS



2.1 Initial assessment of clinical effectiveness

Generalisability of clinical trials

Gene therapies have so far mainly targeted rare conditions, thereby offering treatment opportunities for groups of patients for whom there have traditionally been limited treatment options. By definition, the small patient population size of these conditions means that recruitment to clinical trials is difficult and time-consuming, often resulting in small sample sizes and/or extended timelines for clinical trials (Coyle et al., 2020; Pearson, 2019; Drummond et al., 2019; Aballéa et al., 2020; Hercher and Prince, 2018; van Overbeeke et al., 2021; Jönsson et al., 2019; Huygens et al., 2021; Qiu, Dabbous and Borislav, 2021; Persson and Norlin, 2020; Marsden and Towse, 2017; Abou-El-Enein, Grainger and Kili, 2018; ten Ham et al., 2020). As a result, sample sizes of the trials needed for regulatory approval should not be compared to sample sizes for more common conditions. Yet, the challenge this causes in generating sufficient clinical evidence of efficacy for gene therapies has posed problems for HTA bodies (Hercher and Prince, 2018). Small total patient populations also mean that participants with different baseline characteristics are recruited, with insufficient numbers to define or observe treatment response in clear patient subgroups. The resulting heterogeneity in the clinical trial sample makes treatment response difficult to predict (van Overbeeke et al., 2021). This thereby reduces the generalisability and transferability of effectiveness estimates (Drummond et al., 2019; Persson and Norlin, 2020; van Overbeeke et al., 2021). Some of the diseases targeted by gene therapies may also take different forms as patients age, resulting in heterogeneity in the patient's response to the treatment at different ages and stages of disease progression (Jönsson et al., 2019).

The specialist expertise required for the administration of many gene therapies results in trials often being carried out at specialised facilities. This means that some patients have to travel to participate in the trial, introducing sample selection bias through the inclusion of only those who are willing and able to travel to the specialist facility (Qiu, Dabbous and Borislav, 2021).

For some treatments, the delivery protocol may impact effectiveness. For example, if delivered through a surgical procedure, outcomes may depend on the skill of the surgical team (Marsden and Towse, 2017), reducing the generalisability of results beyond the surgical teams used in the trial.

Given the rarity of the disease areas that gene therapies target, there is sometimes little information on some aspects of the patient population or their treatment pathway/disease progression. For example, there may be a lack of resource estimates for existing clinical pathways (Marsden and Towse, 2017), no patient reported quality of life data available (Huygens et al., 2021) and uncertainty regarding patient epidemiology, burden of disease, and natural history of the disease (Faulkner et al., 2019). These all-present challenges for generating evidence and demonstrating the added value of new gene therapies.

Trial design: alternatives to RCTs

Gene therapies are frequently assessed in single-arm trials (Coyle et al., 2020; Drummond et al., 2019; van Overbeeke et al., 2021; Lloyd-Williams and Hughes, 2020; Jönsson et al., 2019; Garrison et al., 2021; Abou-El-Enein, Grainger and Kili, 2018; ten Ham et al., 2020). The use of these as opposed to randomized controlled trials (RCTs) arises for two main reasons:

Firstly, there is often difficulty identifying an appropriate comparator. This can result from there being no treatment comparator available for the disease, as is the case for the approximately 95% of rare diseases for which there is no effective treatment available (Kaufmann, Pariser and Austin, 2018), insufficient data on potential comparators, and/or rapidly evolving standards of care (Coyle et al., 2020; Drummond et al., 2019; Aballéa et al., 2020; van Overbeeke et al., 2021; Lloyd-Williams and Hughes, 2020; Faulkner et al., 2019; Jönsson et al., 2019; Persson and Norlin, 2020; Ho et al., 2021; Qiu, Dabbous and Borislav, 2021). Choice of comparator impacts the relative effectiveness of the

treatment (Ho et al., 2021). While the lack of a gold standard comparator treatment demonstrates the unmet need that novel gene therapies can address for rare disease patients, difficulties identifying a comparator makes it harder for HTA bodies to assess the "value" of a gene therapy (Qiu, Dabbous and Borislav, 2021).

Secondly, where there is unmet medical need as there are no alternative treatments available and/or where the disease is deemed to be life-threatening, some consider it unethical to withhold treatment from patients by placing them in a placebo control arm of a trial (Coyle et al., 2020; Drummond et al., 2019; van Overbeeke et al., 2021; Jönsson et al., 2019; Persson and Norlin, 2020). Where the delivery method includes surgery, it can also be deemed unethical to use sham surgeries (Marsden and Towse, 2017). In addition, patients themselves may be reluctant to join RCTs with a placebo control arm (Drummond et al., 2019; Qiu, Dabbous and Borislav, 2021), thereby increasing the difficulties of patient recruitment under the already difficult challenge of small patient populations.

The use of single-arm trials means that an economic evaluation is likely to rely more heavily on observational data or comparison with a patient's own baseline (Jönsson et al., 2019). This presents a challenge for HTA bodies, whose processes and evidence requirements are generally geared more toward more standard treatments and study designs.

To determine the relative effectiveness of treatments, indirect comparisons are sometimes made with the use of network meta-analysis or systematic reviews (Qiu, Dabbous and Borislav, 2021). As noted by Ho et al. (2021), Qui et al. (2021) and Champion et al. (2021), such indirect comparisons may lead to uncontrolled confounding factors that bias the observed treatment effects making it difficult to accurately determine the relative treatment effect.

Despite the challenges, the utility and use of real-world data from observational studies to inform decision-making is necessarily expanding, and its use to inform and improve decision-making for gene therapies should be considered an opportunity. Jørgensen, Hanna and Kefalas (2020) concluded in their review of outcome-based reimbursement of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) (CAR-T cell therapies that can be considered cell-based gene therapies (FDA, 2017a; b)) in major European countries that real-world evidence (RWE) has become an increasingly powerful lever for demonstrating the value of the health benefits of gene therapies. The collection of real-world data, for example, through the expanded use of patient registries, may be an important tool for overcoming some of the challenges in the HTA of gene therapies, including supporting post-approval data collection. They could be used to support observational research or post-launch pragmatic trial designs to overcome limited data on outcomes, adverse events, value, resource use and costs (Jönsson et al., 2019). Bauer et al. (2017) also suggest that the use of patient advisory groups could aid data collection, for example, by aiding recruitment to clinical trials. Furthermore, there may be a case for a more prominent role in shared decision-making between patients and providers.

Appropriate outcome measures

Given the long-anticipated effect of gene therapies, which has the potential to last a patient's lifetime, many clinical trials for gene therapies rely on surrogate endpoints that can be measured in the relatively shorter term to determine the efficacy of a treatment (Drummond et al., 2019; Aballéa et al., 2020; van Overbeeke et al., 2021; Faulkner et al., 2019; Jönsson et al., 2019; Huygens et al., 2021; Qiu, Dabbous and Borislav, 2021; ten Ham et al., 2020). However, there is often limited data to establish links between these surrogate endpoints and long-term clinical outcomes of interest (Coyle et al., 2020; Aballéa et al., 2020), creating uncertainty about the true effectiveness of the treatments on the true outcomes of interest. More research is required to establish the validity of surrogate endpoints (Coyle et al., 2020; Drummond et al., 2019; Corbett et al., 2017).

It is generally accepted that QALYs have a number of shortcomings, particularly in the context of rare diseases, of which many have a genetic origin. However, it is often challenging in rare diseases to

enhance or supplement a QoL instrument such as the EQ-5D. The practical issues for developing health state utilities and patient-reported outcome (PRO) measures are often attributed to difficulty recruiting patients for research due to the small population, heterogeneity in this patient population and lack of knowledge about the disease and its progression relative to more common diseases. A recent study by Nicod et al. (2021) considered NICE appraisals of non-oncology orphan treatments, finding that six out of 24 appraisals did not include any PRO evidence. Additionally, the authors reported that when it was included, it failed to "demonstrate change, capture domains important for patients, or was uncertain" (ibid.).

Additionally, there are challenges arising from measuring quality of life in young children who may be too young to describe their own quality of life (Aballéa et al., 2020). Generic measures of quality of life such as EQ-5D-3L and SF-36 may be deemed inappropriate for children (some adaptations such as the EQ-5D-Y have been developed with a number of published valuation sets and more underway, but there are still some methodological issues to resolve), and the use of caregivers and parents for proxy reports may be unreliable for concepts that require interpretation, such as social functioning and emotional well-being (Aballéa et al., 2020). Moreover, the assumption (which underpins the use of quality-adjusted life years [QALYs]) of mutual independence between quality of life and duration of a health state may not hold for young children as their rapid development means that the utility assigned to a state may not be the same as they age (Aballéa et al., 2020). Aballéa et al. (2020) provide an example of a health state defined by 'ability to walk': while it may be reasonable to assume that a child of 6 months does not lose any utility from being unable to walk, when the child is older (e.g., 2/3 years old) their quality of life is impacted by their inability to walk.

In order to address the issues associated with the measurement of quality of life in children, some preference-based paediatric health-related quality of life measures have been proposed (Aballéa et al., 2020). For rare diseases more generally, Nicod et al. (2021) observed that PRO evidence and health state utility values often failed to demonstrate change or capture domains important to patients, but other forms of evidence were used successfully in some cases, such as patient surveys or input during appraisal committee meetings.

Evidence of a disability paradox has been reported in several therapeutic areas targeted by gene therapies. Also known as disease-state adaptation, the disability paradox is where patients of chronic lifelong diseases rate their quality of life as good or excellent despite being perceived to have a lower quality of life by others without disabilities (Albrecht and Devlieger, 1999). The presence of a disability paradox has been found using a discrete choice experiment, in which haemophilia patients had a higher preference value for 99% of EQ-5D-5L health states compared to the general public (O'Hara et al., 2021). It is important that this phenomenon is considered and accounted for during HTA evaluations.

While the advent of innovative gene therapies with truly transformational potential is relatively new, there is much that can be learnt from the experience of other therapies facing similar challenges. For example, for quality of life considerations in the HTA of rare disease treatments, Nicod et al. (2021) examine the nature of PRO and health state utility evidence, concluding that other forms of evidence and expert input are crucial to support a better appraisal of uncertain or missing evidence. Nicod et al. (2020) consider whether supplemental appraisal/reimbursement processes are needed for rare disease treatments based on an international comparison of country approaches, finding that around 40% of countries' studies use supplemental processes for rare disease treatments. The same group of authors examine the impact of different country processes for appraising rare disease treatments, finding that separate or adapted approaches for rare disease therapies appraisal may facilitate more structured, consistent decision-making and better management of the specificities of those treatments (Whittal et al., 2021).

Differing HTA body/payer evidence requirements

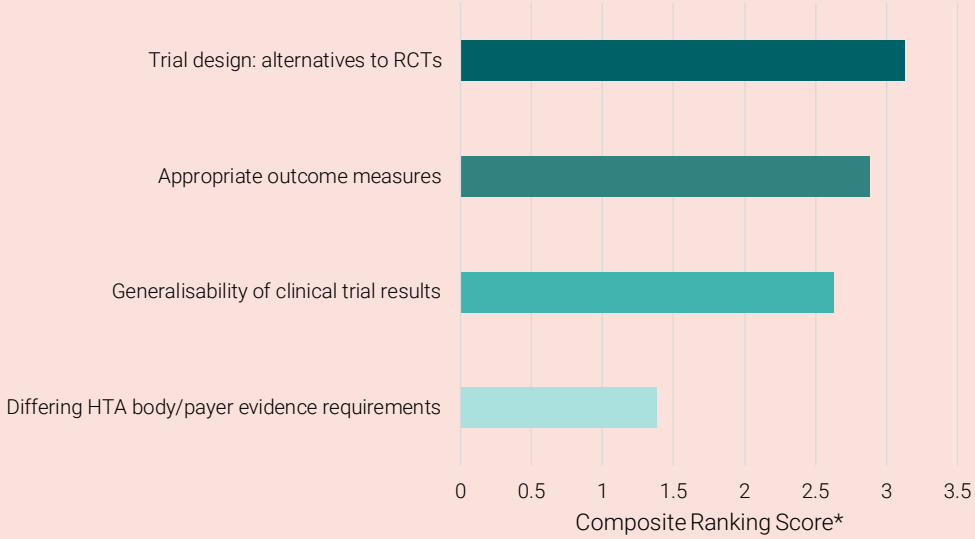
The challenges described in collecting clinical evidence and demonstrating the value of gene therapies are exacerbated by differing HTA evidence requirements between countries, which increase the challenge of designing studies and generating evidence that will be accepted by all HTA bodies (Coyle et al., 2020).

There is, therefore, a call for HTA bodies to be more open and to work with manufacturers to ensure appropriate evidence is collected (Coyle et al., 2020; Qiu, Dabbous and Borislav, 2021). Early dialogue between manufacturers and HTA bodies is particularly helpful in cases of accelerated approval. However, for guidance and established 'best practices' to be most useful to manufacturers, international cooperation and consistency are required (Coyle et al., 2020; Qiu, Dabbous and Borislav, 2021). This is the aim of the European Network for Health Technology Assessment (EUnetHTA) which facilitates collaboration across European HTA bodies. Coordination between HTA bodies and regulators on evidence requirements for both clinical trials and post-authorisation evidence collection (Qiu, Dabbous and Borislav, 2021; Coyle et al., 2020) would also provide clarity for manufacturers and aid alignment on evidence requirements across regulatory and HTA bodies. This is possible through parallel consultations with EMA and EUnetHTA, which enables manufacturers to efficiently consult both regulators and HTA bodies on their evidence generation plans.

Insights from our Expert Panel

Although all the challenges discussed in the literature above are important for the initial assessment of clinical value for gene therapies, our expert panel offered insight into the relative importance of challenges within the theme, ranking the challenge sub-themes, and finding trial design and the use of alternatives to RCTs to be the most important and relevant for HTA of gene therapies.

FIGURE 3: EXPERT RANKING OF THE SUB-THEMES WITHIN THE THEME INITITAL ASSESSMENT OF CLINICAL EFFECTIVENESS



**Where a higher score indicates the challenge was ranked more highly in the orderings made by survey participants.*

Relating to acceptance of evidence by HTA bodies:

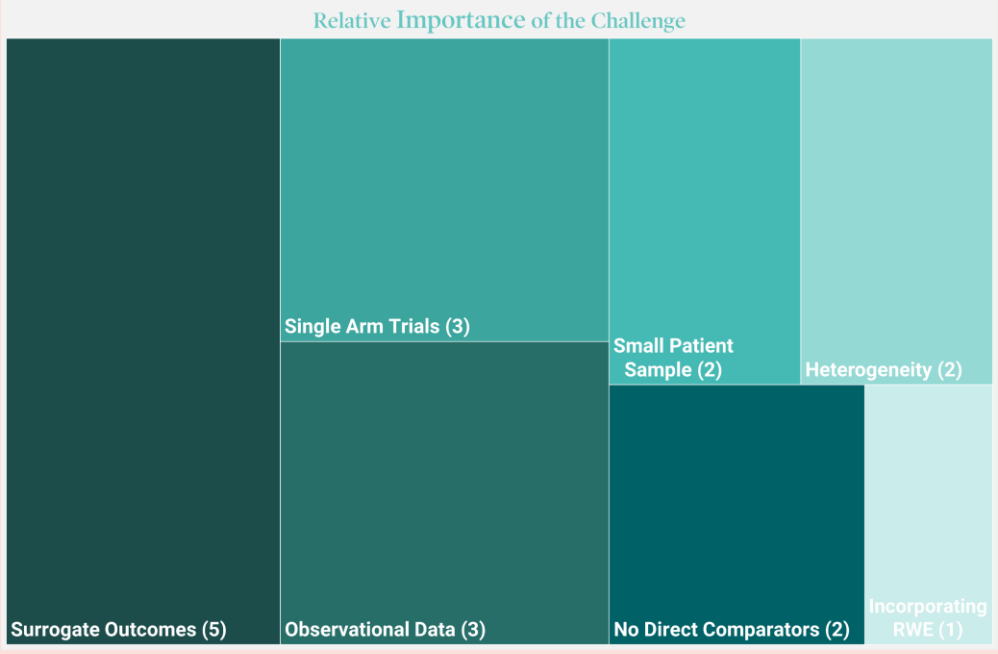
- HTA bodies could develop standards for constructing comparator cohorts to ensure this is completed to a satisfactory standard.

Relating to evidence development:

- As the aim should always be to collect hard endpoints in the long-run, when unvalidated surrogate endpoints are collected during trials, surrogate validation plans should be provided to HTA bodies. This may involve the use of registries to collect data post-approval.
- International collaboration could be used in clinical trial design and recruitment to increase sample sizes. This could also improve the generalisability of results to international contexts.
- Early dialogue between regulators, HTA bodies and manufacturers to clarify the appropriate and proportionate evidence requirements to establish clinical effect.

Figure 4 is a tree map that shows our expert panel's weighting of the relative importance of the more granular challenges within the assessment of clinical effectiveness, where a larger area indicates higher relative importance and numbers in parathesis indicate the number of mentions by our expert panel This revealed that the use of surrogate outcomes, the use of single arm-trials and the use of observational data were ranked most highly as challenges for the HTA of gene therapies, and therefore represent the greatest priority areas.

FIGURE 4: THE RELATIVE IMPORTANCE OF CHALLENGES WITHIN THE THEME INITIAL ASSESSMENT OF CLINICAL EFFECTIVENESS



2.2 Uncertainty regarding long-term outcomes

The potential (lifetime) horizon of the benefits provided by gene therapy treatments, means that the full duration of effect provided by the treatment is often not observed during the follow-up period in the clinical trial (ten Ham et al., 2020), meaning that long-term outcomes are uncertain (Aballéa et al., 2020; Coyle et al., 2020; Pearson, 2019; Hercher and Prince, 2018; van Overbeeke et al., 2021; Lloyd-Williams and Hughes, 2020; Faulkner et al., 2019; Garrison et al., 2021; Jørgensen and Kefalas, 2021; Qiu, Dabbous and Borislav, 2021; Ho et al., 2021; Persson and Norlin, 2020).

The use of surrogate endpoints, as discussed in section 2.1, requires extrapolation of long-term outcomes (Ho et al., 2021; Qiu, Dabbous and Borislav, 2021; Jönsson et al., 2019; Aballéa et al., 2020; Drummond et al., 2019; Marsden and Towse, 2017; Champion et al., 2021) creating additional uncertainty. This often leads to concern among HTA bodies that data are lacking to fully inform model parameters (such as transition probabilities and data on disease progression) (Aballéa et al., 2020), meaning that assumptions need to be made on the basis of little evidence. There is also a lack of consensus on the most appropriate model to extrapolate the short-term outcomes to long-term benefits (Drummond et al., 2019). Judgements will be required if a variety of time horizons are presented for estimates of the duration of the treatment effect (Aballéa et al., 2020; Ho et al., 2021). In this circumstance, a solution could be to consult a range of scientific experts, including disease specialists and geneticists, to establish the likelihood of persistence of the treatment effects over different time horizons.

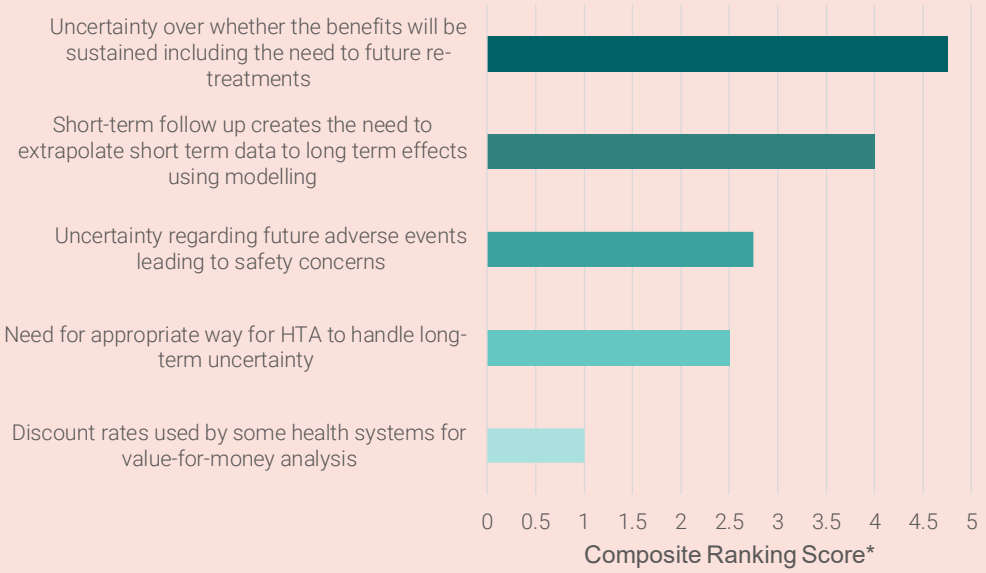
Uncertainty over the durability of treatment effect, and the resulting need for re-treatment in the future (Coyle et al., 2020; Drummond et al., 2019) is also an issue for gene therapies, which can have a large impact on cost-effectiveness. The short-term follow-up of patients relative to the treatment effect also means that data on adverse events may not be available for the entire period in which the individual will potentially be receiving benefits from the treatment and so cannot be included in the analysis (Huygens et al., 2021). This raises potential safety concerns over the use of these new technologies. Enhanced follow-up and monitoring of treated patients over the longer term could help to fill this evidence gap; while this would be beyond the point on an initial HTA appraisal, it could inform a future re-appraisal.

As discussed previously, gene therapies have the potential to accrue benefits to patients across their lifetime, but this means that the benefits will be realised many years into the future. For health systems that consider value for money and apply a discount rate for future benefits, the choice of discount rate is important as it will have a large impact on cost-effectiveness estimates (Coyle et al., 2020; Aballéa et al., 2020; Lloyd-Williams and Hughes, 2020; Jönsson et al., 2019; Huygens et al., 2021; ten Ham et al., 2020). Sensitivity analysis could be used to vary the discount rate to explore the effect that this has on cost-effectiveness (ten Ham et al., 2020; Drummond et al., 2019; Coyle et al., 2020; Huygens et al., 2021). However, to acknowledge the specific challenge in this circumstance that the benefits are realised across a longer time horizon, differential discount rates could be used, for example, using a lower discount rate for benefits than costs (Jönsson et al., 2019).

Insights from our Expert Panel

Our panel of experts ranked the uncertainty over treatment benefits and the uncertain need for future re-treatment as the most important challenge within this theme, followed by the need to extrapolate short-term data using modelling, and uncertainty regarding future adverse events.

FIGURE 5: EXPERT RANKING OF THE CHALLENGES WITHIN THE THEME UNCERTAINTY REGARDING LONG-TERM OUTCOMES



**Where a higher score indicates the challenge was ranked more highly in the orderings made by survey participants.*

Additional context and solutions proposed by the expert panel:

Relating to reducing uncertainty in outcomes during the HTA:

- Use historical cohort data to support predictions regarding long-term outcomes.
- In some circumstances, expert elicitation may be used to describe uncertainties associated with the cost-effectiveness of competing interventions and used to assess the value of further evidence generation. However, it is necessary that expert elicitation is carried out in an appropriate manner to ensure biases are minimized.

Relating to capturing further data after authorization:

- Further use of patient registries to capture longer-term benefits and adverse events.
- Enhanced follow-up through further data collection and re-appraisals.
- Rolling-review style assessment model where evidence is reviewed on a regular basis based on further data collection.

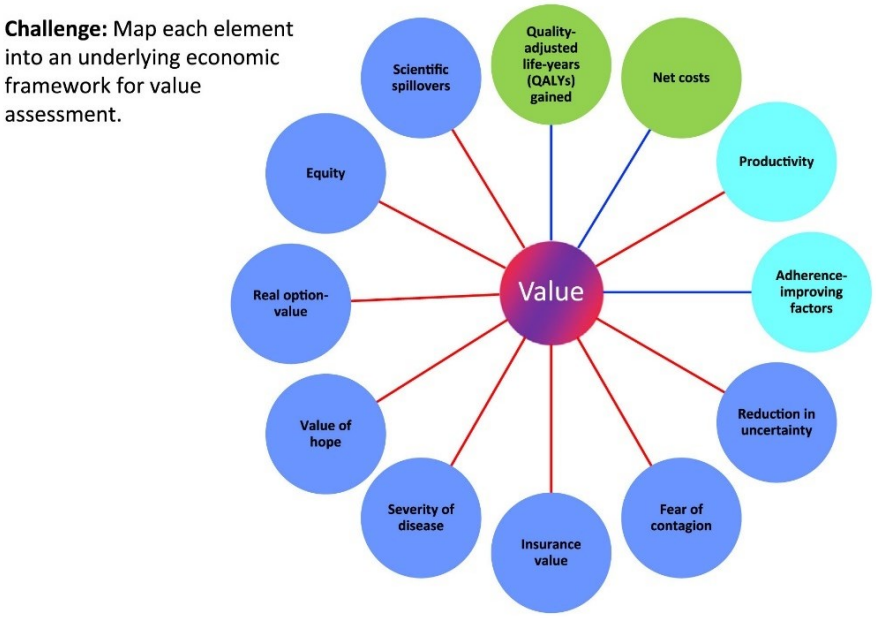
2.3 Incorporating Additional Elements of Value

For health systems that use a cost-per-QALY threshold, the question has also been raised in the literature as to which threshold is the most appropriate (Lloyd-Williams and Hughes, 2020; Coyle et al., 2020; Marsden and Towse, 2017), with suggestions that additional elements of value such as severity of disease may warrant the use of a higher cost-per-QALY threshold for gene therapies.

Society may place a higher value on transformational therapies than iterative improvements in health (Coyle et al., 2020; Aballéa et al., 2020; Jönsson et al., 2019; Marsden and Towse, 2017) which may suggest that a higher cost-per-QALY threshold should be used. However, a discrete choice experiment performed by Hampson et al. (2019) found that although the respondents valued the health gains provided by theoretical cures highly, they did not place additional value on the treatment itself being a cure. The DCE included respondents from the UK only, and as such, the results may not be generalisable to the perspectives of those in other countries.

Many other additional elements of value have been discussed in the literature. The findings of an ISPOR task force present a series of elements they deemed to warrant consideration in value assessments, proposing them in the form of the value flower (Lakdawalla et al., 2018). They found that two elements are considered "core" elements (survival and QoL [QALYs] and net costs), two are common but inconsistently used (productivity and adherence-improving factors) and several are potential novel elements of value (reduction in uncertainty; fear of contagion; insurance value; severity of disease; value of hope; real option value; equity; and scientific spillovers). Some of these additional value elements (with some notable exceptions, such as fear of contagion) are discussed in the literature in relation to gene therapies, along with others, such as potential benefits for caregivers and family, (Jönsson et al., 2019; Huygens et al., 2021; Towse and Fenwick, 2019; Aballéa et al., 2020; Drummond et al., 2019; Pearson, 2019; Coyle et al., 2020; ten Ham et al., 2020). However, it is important to note that the relevance of these additional elements of value is likely to vary between different gene therapies due to the different characteristics of the diseases targeted by them.

FIGURE 6: VALUE FLOWER (LAKDAWALLA ET AL., 2018)

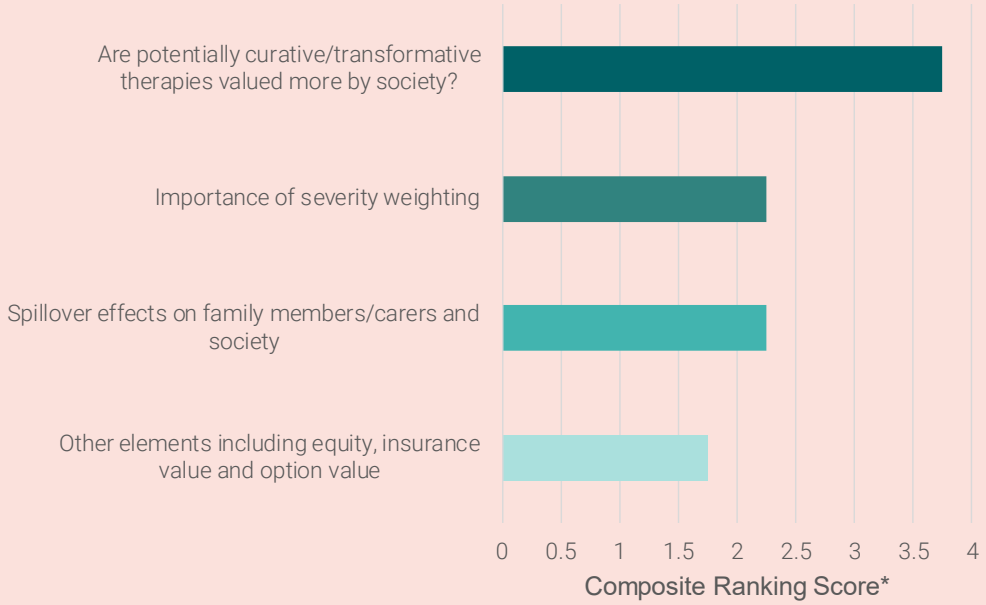


Severity of disease is an important additional element of value, which is considered by HTA bodies in several (but not all) countries. This relates to there being some evidence that society places a higher value on health gains for people with more serious illness, which often coincides with those targeted by gene therapies. Skedgel et al. (2022) elaborate on the empirical evidence in support of the inclusion of severity as well as critically reviewing the state of play of methods currently in use by some HTA bodies. Another related element of particular relevance is spillover effects on family members and carers; improvements in caregiver well-being associated with effective rare disease therapies are important to consider but are infrequently measured and incorporated into value assessments (Jena and Lakdawalla, 2022). Additionally, existing value frameworks do not account

Insights from our Expert Panel

Within the theme of additional elements of value, our expert panel ranked the potential that society values transformative/potentially curative therapies more than iterative improvements as the most important challenge for gene therapies. This is unsurprising given the transformative nature of the therapies and so if society was found to value these more highly, then incorporation of this into HTA methodology could have a large impact on the assessment of gene therapies.

FIGURE 7: EXPERT RANKING OF THE CHALLENGES WITHIN THE THEME ADDITIONAL ELEMENTS OF VALUE



**Where a higher score indicates the challenge was ranked more highly in the orderings made by survey participants.*

Additional solutions proposed by our panel:

- As a first stage, support for HTA bodies in developing their understanding of additional elements of value.
- Structural inclusion of burden (and associated relief) of family and carers in HTA. These additional elements of value are being considered in other contexts but are likely to be very relevant for the diseases targeted by gene therapies.
- In order to incorporate additional elements of value successfully and consistently into decision making, the structure of deliberative decision-making needs to be improved.

for the inherent value of equity: that treatments for those suffering from uncommon diseases with limited treatment options should be prioritized in some way. As defined by the ISPOR Task Force, insurance value (the value of therapies being available, even if it is not likely they would need them), option value (a therapy with long-terms effects that may provide opportunity for the patient to benefit from future technological developments) and value of hope (the idea that severely ill patients may be willing to trade off some survival for a chance of a "cure") may also be particularly relevant for rare disease patients.

Lakdawalla and Phelps (2020, 2021) have developed a theoretical risk-adjusted cost-effectiveness model which incorporates uncertainty and risk aversion for health outcomes, baseline severity and likelihood of cures/value of hope. This approach implies that cost-effectiveness thresholds should vary and that they should be higher for rare, health-catastrophic diseases. However, research into how to measure and derive values such as the relevant utility parameters in health is needed before it can be put into practice.

While these additional elements of value can be included in HTA and/or incorporated into a cost-per-QALY threshold, perhaps through the use of QALY weightings and weightings based on multi-criteria decision analysis (MCDA) (Coyle et al., 2020), this begs the question: which elements of value, over and above health gain for the patient and any health system savings, should be included in the economic evaluation of gene therapies? Different perspectives can be presented to HTA bodies to help demonstrate where the range of the estimated value of the gene therapy lies (Drummond et al., 2019; Garrison et al., 2021). While the additional elements or shortcomings of the QALY can be compensated for in a deliberative decision-making process, different health systems incorporate these perspectives (or not) in different ways. Additional research is required to establish preferences for additional elements of value not currently considered to be appropriately captured in the QALY such as those presented in the value flower (Jönsson et al., 2019; Lakdawalla et al., 2018).

2.4 Assessment of costs

The potential transformative benefits of gene therapies are often reflected by a high price (Hercher and Prince, 2018; Hlávka, Mattke and Wilks, n.d.; Faulkner et al., 2019; Garrison et al., 2021). If the treatments are paid for as they are delivered, the current one dose or short regime nature of gene therapies results in the potential long-term health gains (as well as any potential health system savings), which may last a lifetime, being paid for upfront as opposed to being paid for as they are accrued as with repeat dosage therapy (Marsden and Towse, 2017; Hercher and Prince, 2018; Lloyd-Williams and Hughes, 2020; Huygens et al., 2021; Persson and Norlin, 2020; ten Ham et al., 2020). If therapy is paid for upfront, in the traditional way, this would also mean there are high irrecoverable costs if the treatment is ineffective. (Jørgensen and Kefalas, 2021; Marsden and Towse, 2017). Without innovation in the way that these potentially one-time therapies are paid for, high prices may put pressure on healthcare budgets and risk the sustainability of healthcare systems (Marsden and Towse, 2017; Jørgensen and Kefalas, 2021; Ho et al., 2021).

Another determinant of budget impact is the size of the eligible patient population, which can be uncertain for rare diseases due to limited disease knowledge. In addition, the short-term budget impact of offering the treatment to the prevalent population may be high, although, after this, the treatment of the incident population would be lower. On the other hand, although gene therapies are currently targeting diseases with small populations, they may target more prevalent populations in the future (Coyle et al., 2020). This may create future budgetary pressures if appropriate pricing mechanisms are not set to ensure the long-term affordability of gene therapies.

While the challenge of budget impact relates more to *how to pay* for gene therapies rather than a challenge to *HTA methodology* used to assess them, it is relevant to consider whether budget impact should affect the value-for-money rule used for reimbursement. The challenges of the high costs of gene therapies will produce different responses depending on the health system. In private insurance-based systems, high one-off costs reduces incentives for insurers to cover gene therapies as insurance policyholders may switch providers (Pearson, 2019; Hercher and Prince, 2018; Drummond et al., 2019), meaning that the future cost-savings that may result from reducing ongoing healthcare costs will not accrue to the insurer that funded the initial one-off treatment. This can result in equity issues. In a single payer system, this is not an issue. In addition, if non healthcare costs are included in the HTA, this assumes that the payer also benefits from the cost-offsets that will occur in other sectors of the economy, which may not be the case in practice (but which is more likely in tax-based systems).

In the literature, there is a strong focus on ways to manage this budget uncertainty via the use of innovative payment mechanisms. While the *financing* of gene therapies is out of the scope of this paper, it is pertinent to consider whether the option of paying for therapies in a different way would / could influence the methods or decision outcomes of an HTA body, particularly if these routes to manage budgets can also help to tackle decision uncertainty for the HTA body.

The decisions of HTA bodies to grant patient access to therapies need not be binary; decision uncertainty may be addressed by making recommendations that involve the collection of further evidence. For example, coverage with evidence development grants patients access to the therapy whilst ensuring that additional evidence is collected (Towse and Fenwick, 2019). In addition, recommendations can be restricted to specific patient groups where there is less decision uncertainty.

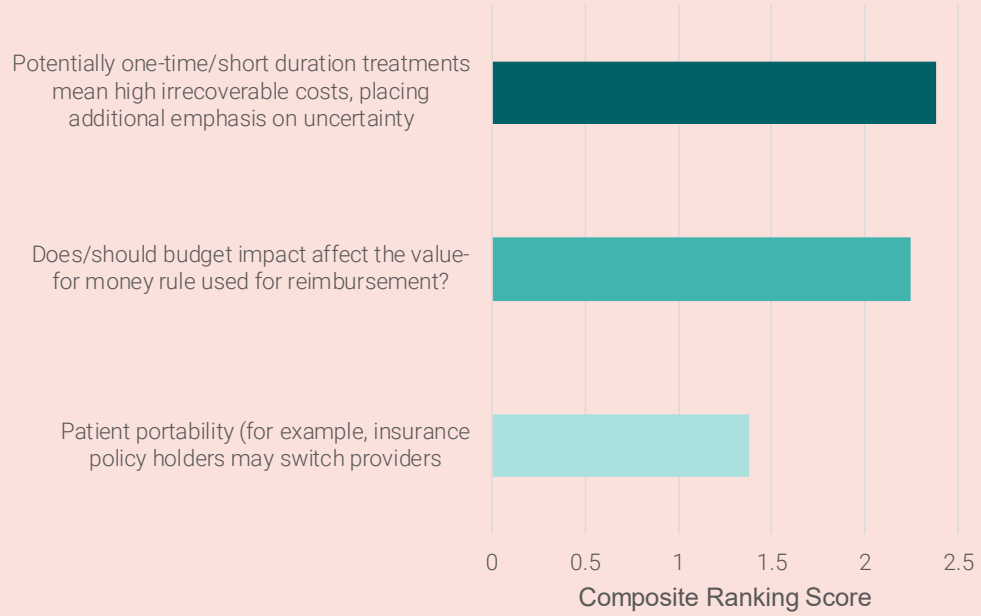
The key relevance of innovative payment mechanisms to HTA is their potential to address decision uncertainty. Outcomes-based arrangements may be used to link payments with outcome, with payment only being provided for the treatment if individual patients or a sample of patients achieve some pre-agreed outcome(s). This addresses the issue of high irrecoverable costs, as if the treatment is no longer deemed effective, the payer stops paying for the treatment. Value of information analysis can be used to inform the arrangements of these agreements (Drummond et al., 2019). These types of performance-linked payment systems increase risk-sharing between payers and manufacturers, but challenges include finding the appropriate outcome measures to inform payments and the requirement of having a good IT infrastructure and data collection (Coyle et al., 2020); implementation of these agreements is still quite rare.

The price obtained for a treatment is an important commercial consideration for manufacturers. Pricing constraints in some health systems may lead to inequity of access, with some manufacturers choosing not to pursue reimbursement in some countries as a result. a. This has occurred in practice with Bluebird's withdrawal of Betibeglogene autotemcel (Zynteglo®) from European markets (Pagliarulo, 2021). In addition, evidence suggests that pricing constraints and more stringent approaches in the face of the uncertainty in clinical effect have resulted in EU4, UK and Canadian HTA bodies tending to recommend access to fewer cell and gene therapies than US health plans (Tunis et al., 2021).

Insights from our Expert Panel

Our expert panel ranked the additional emphasis placed on the uncertainty in clinical outcomes that arises from high irrecoverable costs from the potentially one-shot/short-duration treatments as the most important challenge for gene therapies.

FIGURE 8: EXPERT RANKING OF THE CHALLENGES WITHIN THE THEME ASSESSMENT OF COSTS



**Where a higher score indicates the challenge was ranked more highly in the orderings made by survey participants.*

Additional solutions proposed by our expert panel:

- Due to the potential lifetime benefits and resultant long-term savings that could be generated from potentially curative therapies, budget impact models should have a lifetime perspective and should be updated as new information arises.
- The high costs need to be balanced with the potential broad benefits that accrue over a long period of time and across different budgets. Therefore, there is a need to remove budget silo perspectives in order to appropriately capture costs and cost offsets.
- Use of novel payment models to share risk and spread payments.

Our panel also noted that due to the confidential nature of many managed entry agreements it is difficult to ascertain what methods and agreements have been implemented. This in turn means that it is difficult to assess how different aspects of the agreement are impacting the access to gene therapies and therefore how these agreements could be improved. More could be put in the public domain about the structure of such agreements (while keeping actual price paid confidential), in order to understand good practice.

TABLE 2: SUMMARY OF THE CHALLENGES AND POTENTIAL SOLUTIONS FOR THE IMPROVEMENT OF HTA OF GENE THERAPIES (GTX), CAPTURING THE CONSIDERATIONS FROM BOTH THE LITERATURE AND OUR EXPERT PANEL

	Limitations of current HTA methods: Challenges arising	Potential HTA solutions: Opportunities for GTx
Initial assessment of clinical effectiveness	1. Generalisability of clinical trial results ▪ Small patient populations result in small clinical trial sample size, limiting statistical power ▪ Heterogeneity in the patient population leads to difficulties predicting treatment response ▪ For some treatments: Trials being carried out in specialist facilities could introduce sample selection bias ▪ For some treatments: delivery protocol may impact effectiveness (for example if delivered by surgery, outcomes may depend on skill of surgical team) ▪ Incomplete knowledge on the characteristics of the disease area (for example difficulties identifying an appropriate comparator, or lack of resource estimates for existing clinical pathways)	International Collaboration to increase sample size. Where relative treatment effect is not readily observable with the data and methods available: role for shared decision-making between patients and providers? HTA bodies to provide standards for the use of historical cohorts.
	2. Trial design: alternatives to RCTs ▪ Use of single-arm trials ▪ Indirect comparisons can result in uncontrolled confounding factors that may bias estimation of the treatment effect. ▪ Use of RWE including from observational studies	Early dialogue between stakeholders Improved acceptance and methods to deal with novel trial designs that rely more heavily on observational data. including for example: ▪ Trials with lead-in period: Patient serving as own control ▪ Use of observational data, for example RWE collected in patient registries
	3. Appropriate outcome measures ▪ Reliance on unvalidated surrogate outcomes ▪ Difficulty of getting PROMs (whether converted into QALYs or not) ▪ How to estimate the quality of life in children and individuals with severe disabilities	Broader acceptance of other forms of evidence and expert input regarding treatment outcomes to support better appraisal of uncertain or missing evidence. Aim to collect hard-end points in the long run but where surrogate endpoints are required for use during HTA, validation plans should be provided to HTA bodies. Use of paediatric health related QoL measures, patient surveys and/or patient input during appraisal committee meetings.
	4. Differing HTA body / payer evidence requirements increase the difficulty of designing trials	International cooperation and coordination between HTA bodies as well as regulators on the most appropriate evidence and best practices for gene therapies, including regular review to ensure they are fit-for-purpose and prepared for the innovative medicines of the future.

 Uncertainty regarding long-term outcomes	▪ Short-term follow up creates the need to extrapolate short term data to long term effects using modelling ▪ Uncertainty over whether the benefits will be sustained including whether there will be a need for future re-treatments ▪ Uncertainty regarding future adverse events leading to long-term safety concerns ▪ Need for an appropriate way for HTA to handle this uncertainty ▪ Discount rates used by some health systems for value-for-money analyses	▪ Framework to elicit support from scientific experts to inform model parameters. ▪ Enhanced follow-up and monitoring of treated patients, to inform re-appraisals (or continuous appraisal which may inform a rolling-review process). ▪ Registries to support long-term data collection. ▪ Use of historical cohort data to support predictions regarding long-term outcomes. ▪ Greater acceptance of surrogate endpoints for managed access agreements ▪ Sensitivity analyses of impact of discount rate, and consideration of differential discount rates.
 Incorporating additional elements of value	▪ Are potentially one-time treatments / life changing therapies valued more by society? ▪ Importance of severity weighting ▪ Spillover effects on family members/carers and society ▪ Other elements, including equity; insurance value; option value; value of hope, etc.	▪ Educating the HTA community that value is not limited to health and healthcare. ▪ Incorporation of an assessment of additional value to be part of a deliberative decision-making process within HTA. ▪ Improve the structure of deliberative decision-making. ▪ Structural inclusion of burden (and associated relief) of family and carers in HTA. ▪ Further research to establish the preferences for additional elements of value not currently considered to be appropriately captured in the QALY.
 Assessment of costs	▪ Potential one/short duration treatment(s) means high irrecoverable costs, placing additional emphasis on uncertainty ▪ Uncertain size of patient populations requiring gene therapies ▪ Does / should budget impact affect the value-for-money rule used for reimbursement? ▪ Patient portability (for example, insurance policy holders may switch providers)	▪ Alternative value-for-money criteria based on a threshold level of budget impact. ▪ Lifetime perspective of budget impact models. ▪ Removal of budget barriers and silo perspectives. ▪ Innovative payment models such as outcome-based payments could serve a dual purpose of addressing both budget impact concerns in the short-term and decision uncertainty for HTA. ▪ The combination of payment-by-result methodology and payment in different instalments.

3. HTA of Gene Therapies in Practice

3.1. How the challenges have presented in economic evaluations of gene therapies

Whilst we have not conducted systematic review of the literature or extensive analysis of HTA reports, analysis of this nature has been carried out by other researchers to observe how some of the challenges of the HTA of gene therapies have presented in practice.

Ho et al. (2021) conducted a systematic literature review of the economic evidence on potentially transformative gene therapy products, finding that although all the gene therapies reviewed were deemed effective over their comparators, due to high costs, many were not deemed cost-effective. They reported that gene therapies are more likely to be cost-effective for a condition with high levels of mortality compared with conditions that have a limited impact on lifespan. Given the huge potential benefits of gene therapies for patients, it is pertinent to consider whether the methods applied to deliberate reimbursement decisions are leading to coverage decisions that are optimal for society, thereby sending the right signals for innovation in this space.

In a systematic review of economic evaluations of advanced therapy medicinal products, Lloyd-Williams and Hughes (2021) found evidence to support the cost-effectiveness of axicabtagene ciloleucel, autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (Strimvelis®)[1] and voretigene neparvovec (Luxturna®). However, these estimates are associated with significant uncertainty and a high likelihood of bias, resulting from largely unknown long-term outcomes and paucity of evidence on health state utilities and extensive modelling assumptions.

The modelling assumptions made by HTA bodies have a large impact on cost-effectiveness estimates. Huygens et al's (2021) analysis of HTA decisions by the HTA bodies Zorginstituut Nederland (the Netherlands) and NICE (England) found that the different cost-effectiveness estimates calculated for a variety of assessed gene therapies was driven by different assumptions on the duration of treatment effect, discount rates, sources of utility values and model structures. However, the key challenge for HTA was uncertainty, which was mostly related to the uncertainty in the treatment effect due to long term-effects not being captured in clinical trials (Huygens et al., 2021). Therefore, most HTA body recommendations have included a requirement for longer-term follow-up data from clinical trials and additional data collection via patient registries for use in the reassessment of cost-effectiveness. (Gye, Goodall and De Abreu Lourenco, 2021).

Although a lot of the key challenges described in this report represent general issues that face all HTA bodies that are tasked with assessing new gene therapies, it is important to note that particular challenges or the way they manifest differ between gene therapies and between HTA bodies. Faulkner et al's (2019) systematic review of HTA of regenerative medicines in Australia, Canada, France, the US and the UK illustrates this point. For example, uncertainty regarding duration of effect was noted by all HTA bodies for voretigene neparvovec , alipogene tiparvovec (Glybera®), axicabtagene ciloleucel and tisagenlecleucel , but none for Strimvelis®, and by approximately half of HTA bodies for talimogene laherparepvec (Imlygic®). Other challenges which typically manifest for gene therapy evaluation do not always apply in individual cases, for example although noted by some HTA bodies uncertainty regarding safety was not noted for talimogene laherparepvec and alipogene

[1] Due to the length of the international non-proprietary name (INN) we will refer to autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence by the proprietary name, Strimvelis®, throughout the rest of this report.

tiparvovec , there was no note of an uncertain link between surrogate and hard outcomes for talimogene laherparepvec and Strimvelis®, and no lack of comparative data for voretigene neparvovec and alipogene tiparvovec.

HTA bodies have considered variations to their standard discount rates to consider the long-term nature of the impacts of gene therapies. NICE considered the use of lower alternative discount rates for both costs and benefits in its appraisal of axicabtagene ciloleucel and tisagenlecleuce, tested through sensitivity analyses. However, NICE concluded that there was insufficient evidence to support that treatment effects could be sustained over a very long period (normally at least 30 years) and, therefore, recommended the standard 3.5% discount rate for the reference case (Gye, Goodall and De Abreu Lourenco, 2021). NICE also performed sensitivity analysis of the discount rate in their assessment of voretigene neparvovec (Huygens et al., 2021). Zorginstituut Nederland varied their discount rate using sensitivity analysis in the HTA of voretigene neparvovec but they used differential discounting of 4% for costs and 1.5% for benefits as prescribed by their guidelines (Huygens et al., 2021).

3.2 HTA outcomes for gene therapies

Many HTA bodies have assessed gene therapies, and despite the challenges presented above, some gene therapies have been recommended for use and approved for reimbursement. By considering the differences between HTA bodies in their approach to the evaluation of gene therapies, we can observe what lessons may be learnt and applied to ensure the potential of these treatments can be sustainably realised.

As discussed in the introduction, Table 1 demonstrates the variability in outcomes of HTA of gene therapies across HTA bodies. It has been suggested that this variability is a reflection of uncertainty in the clinical data and HTA bodies' willingness and capacity to deal with the uncertainty (Tunis et al., 2021)(Tunis et al., 2021). As evidenced by the HTA outcomes, positive recommendations of gene therapies are often accompanied by innovative payment mechanisms, coverage with evidence development or restricted indications compared to the EMA approved indication. Some countries where managed entry agreements are already used (e.g., Italy and the UK) have been relatively more successful in securing timely patient access. Jørgensen, Hanna and Kefalas (2020) found that outcomes-based pricing is increasingly being used to facilitate access to gene therapies, particularly in Germany, Spain, and Italy, but that there is a large degree of variability in HTA methodologies across countries. There is no 'one size fits all' solution currently, and they draw attention to the different preferences and priorities of national health system decision-makers.

The same authors provide a detailed review of outcome-based reimbursement of CAR-T cell therapies in major European countries, providing an insight into what might be expected in future for gene therapies. The authors found that tisagenlecleucel and axicabtagene ciloleucel have relatively uniform list prices across the EU4 and the UK and are reimbursed according to their marketing authorisations. In France and the UK, reimbursement is on the condition of collecting additional data (at the cohort level) and subject to future reassessments; elsewhere, rebates (Germany) or staged payments (Italy and Spain) are linked to individual patient outcomes. The experience of these two CAR-T therapies demonstrate an increased appetite for outcomes-based reimbursement (OBR) in the five major European markets, with notably novel approaches applied in Italy and Spain (with outcomes-based staged payments). The authors conclude that real-world evidence (RWE) has become an increasingly powerful lever for demonstrating the value of the health benefits of gene therapies; this sentiment could be carried through to our considerations of the role for on-market evidence generation to influence how and when HTA decisions are made.

Of the additional elements of value already considered by HTA, severity is one of the most widely accounted for. However, there is considerable variation in the methods in place, if any. Some HTA bodies take an explicit approach, including ZiN (the Netherlands), NICE (England), NOMA (Norway)

and TLV (Sweden) (Skedgel et al., 2022). Within these countries, each has a unique approach to accounting for severity, some using absolute shortfall, proportional shortfall or both. Other HTA bodies consider severity implicitly such as ICER in US and Common Drugs Review in Canada. It could also be suggested that considerations for rare diseases can be perceived as implicitly accounted for severity given that rare diseases are usually severely disabling conditions. Other additional value elements are also regularly considered implicitly, particularly innovation and equity/equality (Angelis, Lange and Kanavos, 2018). These considerations, whether implicit or explicit, have almost certainly aided the approval of current gene therapies.

3.3 Case Study: HTA of onasemnogene abeparvovec (Zolgensma®)

In this section, we consider HTA outcomes of onasemnogene abeparvovec (Zolgensma®) in a selection of countries and the various approaches to dealing with uncertainty taken by the HTA bodies. Onasemnogene abeparvovec is a treatment for spinal muscular atrophy (SMA) that is provided in a single infusion (EMA, 2020). It is indicated under EMA approval for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. We selected this gene therapy for our case study because it has been appraised by all but two of the HTA bodies under consideration in this report (reviews are ongoing in Germany and Spain), with each HTA body already having assessed another gene therapy previously, illustrating that despite having experience assessing gene therapies, there are often still improvements to the process that can be made. Additionally, many of the barriers we have detailed above can be seen in the evaluation of onasemnogene abeparvovec, thus highlighting ways in which some potential solutions have been implemented in reality.

Coyle et al. (2020) highlight that due to the rarity of this condition, trials for onasemnogene abeparvovec have very small sample sizes. In addition, due to ethical concerns, the trials are single-arm. Despite these challenges, these single-arm trials have been able to demonstrate gains in survival, milestone achievements and motor function. Here, we present information on the outcomes of HTA of onasemnogene abeparvovec, focusing on the Netherlands (Zorginstituut Nederland); France (HAS); Italy (AIFA); England (NICE) and Canada (CADTH and INESSS).

The Netherlands

In April 2021, the Zorginstituut Nederland (ZIN) advised no reimbursement of onasemnogene abeparvovec, unless a pay-for-performance agreement and very significant price reduction was agreed. It is estimated that a price reduction of at least 50% would be necessary to include onasemnogene abeparvovec in the basic insurance. The report also made reference to the great uncertainty about the long-term effect of the drug. Belgium, Ireland, and the Netherlands were able to reach an agreement on the pricing of onasemnogene abeparvovec (for Type I and pre-symptomatic patients) in October 2021.

France

France's HTA body Haute Autorité de Santé (HAS) issued a positive opinion in favour of reimbursement of Zolgensma® for patients with SMA type I and II or pre-symptomatic. However, they issued a negative opinion for patient with type III SMA due to an absence of data, lesser medical need and non-extrapolable efficacy. The HTA evaluation documents noted the absence of a robust comparison (direct or indirect) of the gene therapy with Spinraza (Nusinersen) (treatment used for management in SMA patients prior to onasemnogene abeparvovec). As a result, it recommended that decisions to initiate treatment are made on a case-by-case basis at multidisciplinary meetings within neuromuscular diseases reference and expert centres belonging to the FILNEMUS network.

Italy

In Italy, reimbursement for onasemnogene abeparvovec uses a "payment at result" contract with checkpoints at 12, 24, 36, and 48 months. As part of the deal, an obligatory discount on the ex-factory price will be applied at public health facilities, including those accredited by Italy's national health service (SSN). Onasemnogene abeparvovec is reimbursed through the SSN for the treatment of all children with SMA Type 1 weighing below 13.5 kg. AIFA's Scientific-Technical Committee (CTS) determined onasemnogene abeparvovec to be an innovative therapy and reimbursement was allowed for patients up to six months of age.

England

Onasemnogene abeparvovec was evaluated by NICE under its Highly Specialised Technologies (HST) pathway. At the time of appraisal, therapies were required to meet strict eligibility criteria to be assessed under the HST process, which included having a licensed indication so small that treatment is provided at very few centres in the NHS, the condition is chronic and severely disabling, likely to have very high acquisition costs and has the potential for lifelong use.[2]

NICE recommended it as an option for treating babies with type I SMA only if they are under 6 months, or, on a case-by-case basis, if they are aged 7 to 12 months. NICE did not use Nusinersen as a comparator because it is not routinely commissioned for use in the NHS (but rather is available via a managed access agreement). The committee noted that there is "very limited evidence for babies with type 1 SMA who are older than 6 months at the start of treatment" and that there was a lack of long-term evidence. The HST pathway allowed for a higher QALY weighting since the lifetime QALYs gained exceeded 10 QALYs (effectively increasing the maximum ICER). Also, a lower discount rate was employed.

Canada

In March 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued a decision to reimburse onasemnogene abeparvovec subject to meeting clinical criteria and/or conditions. The evaluation documents stated that a price reduction of at least 90% was required for onasemnogene abeparvovec to achieve an ICER below $50,000 per QALY gained. As seen in many other HTA evaluations, the lack of direct comparison to Nusinersen was considered a significant limitation. In October 2021, Quebec was the first province to list onasemnogene abeparvovec after the positive recommendation of INESSS (Quebec's HTA body) for children with SMA (on a case-by-case basis).

Sweden

Tandvårds- och läkemedelsförmånsverket (TLV), Sweden's HTA body, assessed onasemnogene abeparvovec and the NT-council received the TLV assessment in February 2021. Due to privacy issues relating to access to the follow-up data, the decision by the NT-council was delayed by a year (i.e. February 2022), resulting in a reduced uptake. The final recommendation for use relied upon a managed access agreement that reduced the one-time cost to align with the company's assumption of lifelong effect.

[2] *NICE has since updated the Highly Specialised Technologies criteria as a result of their topic selection, methods and processes review that took place in 2021. It has removed the requirement for technologies to have the potential for lifelong use in light of the number of one-time therapies coming through the rare disease landscape. More information can be found here: https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies*

Lessons learned

Many of the challenges emerging from the literature as well as the expert panel are reflected in the assessment of onasemnogene abeparvovec. One of the key obstacles to patient access was most HTA bodies' reluctance to accept single-arm trial evidence, despite traditional RCTs being seen as unethica by somel in this circumstance. Early dialogue between stakeholders could have provided an opportunity to align expectations and discuss the practicalities of evidence generation in such a small patient population. Uncertainty in long-term outcomes was a factor in all HTA decisions for onasemnogene abeparvovec, reiterating the need for practical ways to deal with this uncertainty to enable timely patient access. While several HTA bodies required a pay for performance arrangement to be negotiated in order to reimburse onasemnogene abeparvovec, others only recommended treatment on a case-by-case basis or limited the patient population to a smaller subset of patients compared with the full population covered by the marketing authorisation. This case study highlights that there is room for improvement in how gene therapies are assessed under HTA methods to fully realise the potential benefits.

4. Actionable recommendations to address the challenges

Based on our review of the literature, supplemented by the insights and discussions of the expert panel, we arrive at the following six overarching recommendations, which highlight the changes to HTA methodologies as well as evidence generation activities that should be prioritised to enable the potential benefits of gene therapies to be realised. The first two recommendations address challenges in fully capturing the potential value of gene therapies as part of the HTA process. The final four recommendations aim to improve the quality and acceptability of the evidence generated, and to provide methods for handling the residual uncertainty. The recommendations are not specific to the HTA of gene therapies and should be consistently applied across HTA of other treatments. However, due to the combination of challenges presented by the HTA of gene therapies, if implemented, the recommendations are likely to have a larger impact on the assessment of gene therapies.

RECOMMENDATIONS TO BETTER CAPTURE THE VALUE OF GENE THERAPIES:

1. Incorporate methods to recognise the potential lifetime benefits of gene therapies by including a lifetime perspective for in modelling accompanied by sensitivity analysis including of the discount rate.
2. Operationalise additional elements of value as part of the decision-making process within HTA, on the basis of continued research.

RECOMMENDATIONS TO ADDRESS UNCERTAINTY IN OUTCOMES:

3. Develop transparent standards for the inclusion of RWE and surrogate endpoints in HTA.
4. Include outcomes-based arrangements or other value-based arrangements as part of or following HTA to mitigate uncertainty in long term outcomes whilst enabling patient access.
5. Expand data collection through registries and international collaboration.
6. Enable early multi-stakeholder dialogue, including patient representatives, to align on feasible and appropriate HTA evidence packages.

4.1 Incorporate methods to recognise the potential lifetime benefits of gene therapies by including a lifetime perspective in modelling accompanied by sensitivity analysis including of the discount rate.

Gene therapies have the potential to offer long-term benefits for patients by reducing the daily burden of disease management and can lead to cost offsets for health systems through reducing the need for ongoing chronic therapies to manage symptoms. As the potential health benefits and cost offsets are likely to be realised for many years over a patient's lifetime, it is important to assess the impact of the choice of discount rate through the use of sensitivity analysis, due to the large impact that this decision can have on the outcome of the HTA. In addition, due to uncertainty relating to the long-term outcomes, sensitivity analysis of long-term effectiveness of treatments should also be carried out. It is also important to recognise the duration of the cost-offsets through the use of a lifetime perspective for any budget impact models.

4.2 Operationalise additional elements of value as part of the decision-making process within HTA, on the basis of continued research.

At present, HTA bodies vary not only in which additional elements of value they consider, if any, but also in the way they capture them. Several HTA bodies already consider additional value elements implicitly via their deliberative decision-making, which may include equity, innovation/unmet need, rarity, family spillovers and productivity. There are also explicit considerations of additional value elements, such as the use of different thresholds based on severity of disease in Norway and the severity modifier recently introduced by NICE as part of their new updated methodology manual.

There is empirical evidence to suggest that the public is generally supportive of a "severity premium"; this is increasingly reflected in HTA. Due to the severe nature of the rare diseases typically targeted by gene therapies, the inclusion of severity in HTA is likely to impact the HTA of gene therapies. Several HTA bodies, including many of countries considered in this report, consider severity to some extent, but their approaches vary considerably. Whilst the inclusion of severity in HTA has advantages for some therapy areas, it has been argued that current approaches could be improved by using an explicit and quantitative approach (Skedgel et al., 2022). Additionally, the optimal approach is likely to differ depending on a country's existing HTA methods and wider health system.

In comparison to severity, there is less consensus on the incorporation of other elements of value. The nature of conditions that gene therapies typically target means that carer burden can be significant. NICE have previously allowed the inclusion of health effects for informal carers in evaluations and have recently provided a set of minimum evidence requirements. NICE's efforts in this area are promising and may set an example of how carer burden can be incorporated by other HTA bodies.

Lastly, it is generally agreed that not all additional elements should have equal weighting. We suggest that further research is needed to understand which other value elements should be incorporated, to what extent and how.

4.3 Develop transparent standards for the inclusion of RWE and surrogate endpoints in HTA

It is widely accepted that, where possible, RCTs should be used to determine the relative effectiveness of a treatment. However, as it is not always appropriate or possible to carry out RCTs for gene therapies, HTA bodies need to demonstrate flexibility in accepting alternative forms of evidence where appropriate. HTA bodies should be transparent about the circumstances or criteria for accepting observational data (e.g., lack of treatment alternatives, small patient populations [and how that is defined], etc.), and be explicit in the type of RWE they will accept.

Similarly, HTA bodies should recognise that, due to the potential for benefits to accrue over a long period of time, surrogate outcomes may be required in order to enable timely patient access, and stakeholders should work together to generate standards for the validation of surrogate endpoints. This is likely to include a requirement for surrogate validation plans to be agreed with HTA bodies when HTA submissions are made using unvalidated surrogate endpoints. It also needs to be recognized that in some circumstances, surrogate endpoints may need to be chosen to enable historical cohorts to be used to help estimate the treatment effect. HTA bodies should consider being more open to the use of historical cohorts, to be used together with validated surrogate endpoint to estimate treatment effect.

4.4 Include outcomes-based arrangements or other value-based arrangements as part of or following HTA to mitigate uncertainty in long term outcomes whilst enabling patient access.

Value-based arrangements offer a way to permit access while managing uncertainty for payers, for example coverage with evidence development which allows access to gene therapies whilst additional data are collected – allowing uncertainty to be reduced over time - or outcome-based payments which link payment directly with outcomes achieved at the individual patient level. In addition, novel payment terms, such as amortisation (i.e., paying regular payments over a longer time period), can also help to address payers short-term budget impact concerns. However, with all such payment models, it can be challenging to negotiate mutually agreeable terms, and appropriate data infrastructure is required.

4.5 Expand data collection through registries and international collaboration

Registries are important for both providing evidence of initial clinical effectiveness and for providing the infrastructure for post approval evidence generation to address uncertainties.

Registries should be designed to provide data to enable greater understanding of patients and diseases, including patient histories, disease progression and existing clinical pathways. However, the market is unlikely to undertake this task alone, due to the lack of incentives, suggesting that government or charitable intervention may be required. In France, in order to expand data collection, as part of the French National Rare Disease Plans (PNMR) a national database of Rare Diseases (BNDMR) has been established (FIMATHO, 2022). Their aim is to link this data base with the claims database to increase information on the history of rare diseases in France and the current clinical pathways.

International collaboration on patient registries is particularly important in the rare disease space, where patient numbers are small. International collaboration would allow for richer data to be produced, increasing the usability of datasets. However, international collaboration on datasets can be difficult and requires careful consideration due to data protection laws. International collaboration may also help to find historical cohorts to accompany single arm trials and even to provide information on long-term outcomes. The European Medicine's Agency (EMA) is aiming to help collaboration on registries and avoid duplication of efforts by providing an inventory of registries (EMA, 2018). This has been supported through EMA workshops that include guidance for setting up registries to enable collaboration, including using consent that enables data sharing.

Where disease registries do not exist, and are not possible for the manufacturer to develop, patient registries for the treatment should be established at the point of early dialogue between stakeholders i.e., regulators and manufacturers. This may enable the follow-up period to be shortened, reducing the amount of time for which uncertainty regarding long-term outcomes is present.

4.6 Enable early multi-stakeholder dialogue to align on feasible and appropriate evidence packages

Key stakeholders should engage in dialogue before evidence generation begins to determine what evidence packages are feasible and appropriate. Manufacturers should engage with regulators, HTA bodies and where possible, patient groups.

This could be achieved via formal networks such as EUnetHTA which offers parallel consultations between European HTA bodies and regulators (EMA). Or alternatively, if available, consultation pathways offered directly by HTA bodies such as CADTH's scientific advice program or NICE's scientific advice service and Office for Market Access. The dialogue generated and advice received will facilitate manufacturers to integrate HTA and regulatory needs in their development plan. These

pathways often prioritise therapies that target a life-threatening or chronically debilitating disease and responds to unmet need, which could be especially pertinent for gene therapies.

Early stakeholder dialogue will facilitate discussion and negotiation on the feasibility of carrying out an RCT or, if this is agreed to be unethical or unfeasible, then parties can align on collection of observational data. A key aspect to be discussed is minimum standards for prospective data collection including RWE, which should also include input from patients on the most relevant outcomes to them. Historically, primary outcomes have been focused on clinical status and have not fully captured the impact on patients. While quality of life measures are routinely collected, patient meaningful outcomes often go beyond this to include impacts on their independence, education/employment and family life.

5. Conclusion

Overall, current HTA methodologies are a good starting point for assessing gene therapies. However, there are a significant number of limitations and variability in the way current HTA methods capture, reward, and therefore incentivize the development of gene therapies for the treatment of rare diseases, which in practice has led to variable HTA outcomes and therefore variable patient access. Some HTA bodies have specific pathways for rare disease which have enabled access to gene therapies. However, due to the overall approach of some HTA bodies, these specific pathways may not be feasible in all countries. In addition, future gene therapies may target diseases that would not fall within these rare disease pathways, meaning that these may not be a long-term solution to overcoming the challenges presented by the HTA of gene therapies.

The recommendations we make in this report aim to address the current challenges, and while all recommendations hold relevance for the HTA of gene therapies, many also reflect a broader and ongoing debate about how best to advance and evolve HTA. While considerable progress can be observed in the practices of global HTA bodies, the solutions are inconsistently applied resulting in variable and inconsistent decisions and, most significantly, variable patient access. Therefore, in this report we have proposed six recommendations that will better enable HTA bodies to capture the value of gene therapies more routinely and to encourage evidence generation to support current HTA methodologies. Different countries are at different stages towards achieving these recommendations, but the aim is that if these are consistently applied, they will enable the potential health gains from gene therapies to be realized.

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- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

CONSULTING | REPORT
JUNE 2022

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OHE is a Charity Registration No. 1170829
Registration Office Southside, 105 Victoria Street, London SW1E 6QT