



# Evaluation of Advanced Therapy Medicinal Products by the National Institute for Health and Care Excellence (NICE): An Updated Review

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## Abstract

This review discusses the methodological challenges to the evaluation of advanced therapy medicinal products (ATMPs) by the UK National Institute for Health and Care Excellence (NICE). We analysed the health technology appraisals (both published and in development) of ATMPs conducted by NICE in England until July 2021. A total of 14 health technology appraisals of ATMPs were included, of which two were in development and 12 had been published. There were ten gene therapy products (talimogene laherparepvec [TA410], strimvelis [HST7], tisagenlecleucel [TA554 and TA567], axicabtagene ciloleucel [TA559], voretigene neparvovec [HST11], autologous anti-CD19-transduced CD3+ cells [TA677], betibeglogene autotemcel [ID968], onasemnogene abeparvovec [HST15] and OTL-200 [ID1666]), one tissue engineered product (holoclar [TA467]) and three somatic cell therapy products (darvadstrocel [TA556] and autologous chondrocyte implantation [ACI] [TA477 and TA508]). Only three of these technologies were not recommended by NICE, although four were only recommended within the Cancer Drugs Fund. There was large uncertainty in the assessment of clinical effectiveness, as evidence relied mostly on small, single-arm, open-label studies. There were also several concerns in the cost-effectiveness evaluations, such as limited information on health-related quality of life, immature survival data due to short follow-up, and unclear curative potential. Substantial risk may be incurred with ATMPs, which have high upfront and possibly irrecoverable costs but uncertain long-term benefits. In conclusion, the challenges raised by the economic appraisal of ATMPs, albeit not unique, may be exacerbated by the uncertainty related to the often scant evidence base. Adaptations of the conventional decision-making process rather than completely new methods may improve appraisals of ATMPs.

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### Key Points for Decision Makers

Advanced therapy medicinal products have transformative potential, but the limited evidence available presents significant challenges to economic evaluation.

Evaluation of advanced therapy medicinal products is pervaded with uncertainty because of the lack of robust evidence in many key aspects. However, conventional methods of health technology appraisal employed by the UK National Institute for Health and Care Excellence may still be applied with some adjustments and perhaps greater flexibility than for other technologies.

Considering the methodological uncertainty in cost-effectiveness appraisals and the potential for irrecoverable costs for health systems, decision makers may wish to consider new contractual arrangements that enable access to novel technologies whilst sharing the risks between health systems and pharmaceutical companies.

## 1 Introduction

Advanced therapy medicinal products (ATMPs) are medicines that replace or regenerate human cells, tissues or organs to restore or establish normal function. The European Medicines Agency (EMA) identifies three groups of ATMPs: gene therapy products, tissue engineered products and somatic cell therapy products [1]. In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs (e.g., cells embedded in a biodegradable matrix or scaffold).

Although potential breakthroughs in this area of clinical research are eagerly anticipated, unregulated use of novel therapies with unproven benefits can be not only ineffective but also potentially harmful [2]. Furthermore, technology evaluations of ATMPs may present additional challenges compared with those of conventional pharmaceutical treatments, and straightforward application of standard appraisal methods recommended by the UK National Institute for Health and Care Excellence (NICE) might be difficult or even inappropriate [3]. Acknowledging the need for flexible and adaptable methods to ensure that innovative technologies, such as ATMPs, are “fairly, efficiently and robustly” evaluated, NICE is currently considering substantial changes to its methods of health technology evaluation [4]. The aims of this study are to review evaluations of ATMPs conducted

by NICE and discuss the associated challenges and methodological issues.

## 2 Methods

We searched for appraisals of ATMPs, both published and in development, on the NICE database of technology appraisal guidance [5] and highly specialised technologies guidance in July 2021 [5]. We cross referenced this with the list of ATMPs published by the EMA [6]. For each technology, we reviewed the final appraisal or evaluation determination document and associated documents. We extracted data about several domains pertaining to clinical effectiveness and cost effectiveness, broadly following the structure recommended by the guide to the process of technology appraisal published by NICE (clinical effectiveness, cost effectiveness, uncertainty, discounting, subgroups, additional benefits, generalisability to the national health service [NHS], innovation, service reformulation, inequalities, patient access schemes, end of life) [7]. ATMPs for which marketing authorisation was withdrawn were not considered eligible for this study.

## 3 Results

To date, NICE has published guidance on 14 ATMPs (Table 1): ten gene therapy products (talimogene laherparepvec [TA410] [8], strimvelis [HST7] [9], tisagenlecleucel [TA554 and TA567] [10, 11], axicabtagene ciloleucel [TA559] [12], voretigene neparvovec [HST11] [13], autologous anti-CD19-transduced CD3+ cells [TA677] [14], betibeglogene autotemcel [ID968] [15], onasemnogene abeparvovec [HST15] [16] and OTL-200 [ID1666] [17]), one tissue engineered product (holoclax [TA467] [18]) and three somatic cell therapy products (darvadstrocel [TA556] [19] and autologous chondrocyte implantation (ACI) [TA477 and TA508] [20, 21]). The appraisal of sipuleucel-T was excluded since the guidance and associated documents were removed when the EMA withdrew marketing authorisation [22].

Seven of these contained positive recommendations for use in specific indications (talimogene laherparepvec, strimvelis, voretigene neparvovec, holoclax, onasemnogene abeparvovec and the two ACI), four recommended that the ATMP should be included in the Cancer Drugs Fund (CDF) (tisagenlecleucel, axicabtagene ciloleucel and autologous anti-CD19-transduced CD3+ cells) and three did not recommend the ATMP for use in the NHS (darvadstrocel, betibeglogene autotemcel and OTL-200).

The incremental cost-effectiveness ratios (ICERs) for ATMPs recommended under the technology appraisal guidance [5] were within the £20,000–30,000 per

**Table 1** Summary of characteristics of the advanced therapy medicinal products included in this review

Number and ATMP name	Tisagenlecleucel [TA 554]	Axicabtagene ciloleucel [TA 559]	Tisagenlecleucel [TA 567]
Conditions	B-cell acute lymphoblastic leukaemia	Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma	Diffuse large B-cell lymphoma
Recommendation	Tisagenlecleucel therapy is recommended for use within the CDF as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged ≤ 25 years, only if the conditions in the managed access agreement are followed	Axicabtagene ciloleucel therapy is recommended for use within the CDF as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed	Tisagenlecleucel therapy is recommended for use within the CDF as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed
Type of AMT	CAR T-cell therapy	CAR T-cell therapy	CAR T-cell therapy
Administration and cost	Single dose £282,000	Single dose but price not known	Single dose £282,000
Clinical effectiveness	Tisagenlecleucel is clinically effective, but the benefit vs. blinatumomab or salvage chemotherapy is based on naïve indirect comparisons as direct comparator data are lacking	Axicabtagene ciloleucel is clinically effective, but the lack of comparator data makes assessing comparative effectiveness challenging	Tisagenlecleucel is clinically effective, but immature survival data and the lack of trial data directly comparing tisagenlecleucel with salvage chemotherapy means the size of this benefit is difficult to establish. Tisagenlecleucel is associated with frequent AEs, and the costs associated with managing and treating these should be reflected in the cost-effectiveness modelling
Cost effectiveness (ICER)	Over £30,000 per QALY for blinatumomab Over £45,000 per QALY for salvage chemotherapy	Over £50,000 peer QALY for salvage chemotherapy	£42,991 per QALY gained with a 2-year cure point, £49,963 per QALY gained with a 3-year cure point, £55,403 per QALY gained with a 4-year cure point
Uncertainty	Only three single-arm studies (phase II) with small sample sizes and different populations that are difficult to compare. Uncertainty about whether and how many pts would need an allogeneic stem cell transplant after tisagenlecleucel. Lack of data to determine the costs of treating side effects. Lack of valid and reliable data on survival beyond 30 months and curative effect	Data from a small single-arm study (phase I/II) and data for comparators are of low quality. Limited follow-up and no direct data comparing axicabtagene ciloleucel with salvage chemotherapy. Uncertainty in extrapolation of long-term survival and cure points. Uncertainty about whether and how many pts will need intravenous immunoglobulin	Data from single-arm study with short follow-up and a small observational study. Lack of reliable data on long-term survival and cure points. Lack of data about need for intravenous immunoglobulins for B-cell aplasia and stem cell transplant
Discounting	3.5% for costs and benefits	3.5% for both costs and benefits immature, so the duration of health benefits cannot robustly show cure	3.5% for both costs and benefits
Subgroups	Numbers too small to analyse Philadelphia chromosome positive and negative separately	No mention	Considered those not eligible for stem cell transplant, but this population is difficult to define
Additional benefits	No benefits beyond those captured by QALY calculation	No benefits beyond those captured by QALY calculation	No benefits beyond those captured by QALY calculation
Generalisability to NHS	Uncertain generalisability to routine practice in the NHS	Generalisable to patients and clinical practice in the NHS	Findings are generalisable to clinical practice in the NHS
Innovation	Innovative treatment, but reference case still applicable	Innovative treatment, but reference case still applicable	Innovative treatment, but reference case still applicable

Table 1 (continued)

Number and ATMP name	Tisagenlecleucel [TA 554]	Axicabtagene ciloleucel [TA 559]	Tisagenlecleucel [TA 567]
Service reformulation/ change in practice	Not discussed	Will need a phased implementation in the NHS due to new infrastructure and training required to administer treatment and manage side effects	Not discussed
Inequalities	No issues identified	No issues identified	No issues identified
PAS	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence. The most plausible cost-effectiveness estimates for tisagenlecleucel are above what is considered an acceptable use of NHS resources, so it is recommended for use within the CDF to collect further data on subsequent stem cell transplant rates and immunoglobulin usage	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence. The most plausible cost-effectiveness estimates for axicabtagene ciloleucel vs. salvage chemotherapy are above what is considered an acceptable use of NHS resources, so it is recommended for use within the CDF to collect further data on PFS, OS and immunoglobulin usage	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence. ICER higher than what is considered an acceptable use of NHS resources, so recommended for CDF to collect more data on PFS, OS and immunoglobulin usage
End of life	Tisagenlecleucel extends OS by > 3 months, but it cannot be considered a life-extending treatment at the end of life as the life expectancy of people with relapsed or refractory acute lymphoblastic leukaemia is uncertain	Axicabtagene ciloleucel meets both criteria to be considered a life-extending treatment at the end of life	Tisagenlecleucel meets both criteria to be considered a life-extending treatment at the end of life
Number and ATMP name	Talimogene laherparepvec [TA 410]	Holoclax [TA 467]	Darvadstrocel [TA 556]
Conditions	Unresectable metastatic melanoma	LSCD after eye burns	Complex perianal fistulas in CD

Table 1 (continued)

Number and ATMP name	Talimogene laherparepvec [TA 410]	Holoclar [TA 467]	Darvadstrocel [TA 556]
Recommendation	Talimogene laherparepvec is recommended in adults as an option for treating unresectable, regionally or distantly metastatic (stage IIIB, IIIC or IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if: -Treatment with systemically administered immunotherapies is not suitable and -The company provides talimogene laherparepvec with the discount agreed in the PAS	Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is recommended as an option for pts with moderate to severe LSCD after eye burns, only if: -It is only used to treat one eye and -Pts have already had a conjunctival limbal autograft or -There is not enough tissue for a conjunctival limbal autograft, or it is contraindicated and -The company provides it with the discount agreed in the PAS. Moderate to severe LSCD is defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity. Holoclar is recommended in people with moderate to severe LSCD after eye burns for treating both eyes only: -In the context of research and -When there is not enough tissue for a conjunctival limbal autograft. Such research should be designed to generate robust evidence of the clinical and cost effectiveness of Holoclar in treating two eyes in pts without enough tissue for a conjunctival limbal autograft	Darvadstrocel is not recommended, within its marketing authorisation, for previously treated complex perianal fistulas in adults with non-active or mildly active luminal CD
Type of AMT	Modified form of the herpes simplex virus type-1 that kills cancer cells	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Allogeneic stem cells
Administration and cost	Administered by intravesical injection at an initial dose of 1,000,000 PFU/mL, followed by doses of 100,000,000 PFU/mL at 3 weeks and then every 2 weeks. The acquisition cost of talimogene laherparepvec is £1670 per 1 mL vial of either 1,000,000 or 100,000,000 PFU/mL (excluding VAT)	Single treatment for one eye costs £80,000 excluding VAT	Single dose (up to three fistula tracts) costs £54,000
Clinical effectiveness	Evidence presented was insufficient to draw firm conclusions about the relative clinical effectiveness of talimogene laherparepvec vs. ipilimumab because the trial used a comparator widely considered ineffective and not used in the NHS. Improved toxicity profile vs. ipilimumab	Holoclar is an effective treatment, but uncertainty remains about the comparator success rates and the comparative effectiveness of Holoclar	Data on clinical effectiveness of darvadstrocel showed only modest benefit over and above placebo. Clinical benefit to pts in the NHS is unknown. A 14% additional remission rate is disappointing for a highly complex, one-off treatment that is associated with high upfront costs. The EMA considered that further information on efficacy was necessary, and the marketing authorisation is subject to the submission of the results of an ongoing trial with a larger number of pts and a global registry

Table 1 (continued)

Number and ATMP name	Talmogene laherparepvec [TA 410]	Holoclar [TA 467]	Darvadstrocel [TA 556]
Cost effectiveness (ICER)	£23,900 per QALY gained against dacarbazine and £24,100 per QALY gained against BSC in pts whose disease was not suitable for treatment with systemically administered immunotherapies	Conjunctival limbal allograft from a living related donor: £42,139 (one eye) or £63,047 (two eyes) per QALY. Keratolimbal allograft: £30,415 (one eye) and £69,455 (two eyes) per QALY. BSC: £6948 (one eye) and £12,669 (two eyes) per QALY. If the effect on the donor was taken into account, the ICERs for Holoclar would likely decrease and fall within the range of £20,000–30,000 per QALY gained. Given pt need and the innovative nature of the treatment, the committee agreed that it would pragmatically accept this as a demonstration of cost effectiveness	£23,176–143,131 (estimates are highly uncertain) per QALY
Uncertainty	Evidence of low quality for clinical effectiveness as based on post-hoc analysis of a subgroup in a single RCT. Risk of bias due to limited blinding and differential loss of follow-up. Comparator was not representative of standard care and not available in the NHS. Lack of reliable and valid data for comparison with ipilimumab (the most adequate comparison for equivalent disease stage in the NHS). Lack of data on clinical effectiveness against comparator for similar disease stage means that cost effectiveness overall could not be assessed. Company largely overestimated survival in the economic model	Three studies with follow-up of ≤12 months, and five studies with follow-up of 12 months up to 14.5 years. Uncertainty in the assumptions about the long-term success rates of comparators and the use of eyedrops. Uncertainty about long-term success of Holoclar, so if transplant was successful at 1 year, lifelong success was assumed. No data for two eyes	One single RCT with only 1-year follow-up, so the duration of benefit is uncertain. Lack of valid data on PROs; no data on HRQoL for CD with complex fistula. Lack of data on relapse rates and time to relapse after remission to understand impact on natural history of disease
Discounting	3.5% for both costs and benefits	3.5% rate for costs and benefits to be applied as LSCD is not a fatal or near-fatal condition	3.5% for both costs and benefits because there is uncertainty about long-term effects and impact on HRQoL
Subgroups	Clinical and cost-effective option only for pts for whom systemic immunotherapy is unsuitable	Holoclar was only cost effective for treating one eye, but recommendations apply to unilateral and bilateral disease	Not considered but, in any case, it was only considered for pts similar to those in the RCT
Additional benefits	No benefits beyond those captured by QALY calculations	Potentially negative effects on the donor (in case of conjunctival limbal allograft transplantation) and donor eye (in case of conjunctival limbal allograft transplantation) were not captured	No comment
Generalisability to NHS	Not directly addressed but comment that it would be suitable for pts for whom alternative localised treatments are not widely available in the NHS	Results for Holoclar are plausible, but results for comparators are uncertain	Uncertain generalisability to pts who receive contemporary management in the NHS, as outcomes of placebo arm were better than expected in the NHS
Innovation	Innovative treatment, but reference case still applicable	Innovative treatment, but reference case still appropriate	Innovative treatment, but reference case still applicable
Service reformulation/change in practice	Not discussed	No comment	No comment

Table 1 (continued)

Number and ATMP name	Talmogene laherparepvec [TA 410]	Holoclar [TA 467]	Darvadstrocel [TA 556]
Inequalities	No issues identified	No issues	No issues
PAS	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence	Company has a commercial arrangement (PAS) that would apply if the technology were recommended
End of life	The case for end-of-life considerations was not made	Not applicable	No comment
Number and ATMP name	ACI [TA 477]	ACI using chondrosphere [TA 508]	Autologous anti-CD19-transduced CD3+ cells [TA677]
Conditions	Symptomatic articular cartilage defects of the knee	Symptomatic articular cartilage defects of the knee	Relapsed or refractory mantle cell lymphoma
Recommendation	<p>ACI recommended as an option for treating symptomatic articular cartilage defects of the knee only if:</p> <ul style="list-style-type: none"> <li>-Pt has not had previous knee repair surgery</li> <li>-Osteoarthritic damage to the knee is minimal (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis)</li> <li>-Defect is &gt; 2 cm<sup>2</sup></li> <li>-Procedure is done at a tertiary referral centre</li> </ul>	<p>ACI using chondrosphere is recommended as an option for treating symptomatic articular cartilage defects of the knee in adults only if:</p> <ul style="list-style-type: none"> <li>-Pt has not had previous surgery to repair articular cartilage defects</li> <li>osteoarthritic damage to the knee is minimal (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis) and</li> <li>-Defect is &gt; 2 cm<sup>2</sup></li> </ul>	<p>Treatment with autologous anti-CD19-transduced CD3+ cells is recommended for use within the CDF as an option for treating relapsed or refractory mantle cell lymphoma in adults who have previously had a BTK inhibitor. It is only recommended if the conditions in the managed access agreement for autologous anti-CD19-transduced CD3+ cells treatment are followed</p>
Type of AMT	Traditional ACI or matrix-associated chondrocyte implantation	Autologous chondrocytes combined in a scaffold (chondrospheres)	CAR T-cell therapy
Administration and cost	Costs may vary in different settings because of negotiated procurement discounts. Recommendations are based on a maximum cell cost of £16,000	£10,000 per culture per pt, including cell costs and transportation. Costs may vary in different settings because of negotiated procurement discounts	Price was submitted as commercial in confidence
Clinical effectiveness	Although uncertain, there is some evidence that ACI improves symptoms over 2–5 years vs. microfracture (the most suitable comparator). ACI works better when there has been no previous knee repair and there is no osteoarthritic damage, and microfracture is not suitable for defects >2 cm <sup>2</sup>	Chondrosphere is at least as effective as microfracture at 2 years for defects of 1–4 cm <sup>2</sup> , with a greater difference observed in defects > 2 cm <sup>2</sup> up to 4 cm <sup>2</sup> . Chondrosphere improves outcomes at 4 years and for larger defects vs. microfracture	Preliminary evidence suggests that pts may live for longer and have more time before their disease relapses
Cost effectiveness (ICER)	ICER for the whole eligible population may exceed £20,000 per QALY gained but likely to be under £20,000 per QALY gained for subgroups	When microfracture is assumed to return to baseline utility values after 5 years, the ICERs are £4360 per QALY gained for chondrosphere only vs. microfracture only and £5294 per QALY gained for chondrosphere followed by chondrosphere vs. microfracture only. ICER for chondrosphere vs. BSC is likely to be < £20,000 per QALY gained, for defects > 2 cm <sup>2</sup>	ICER (with discount agreed in the commercial arrangement) likely to range between £46,898 and £72,920 per QALY gained, but committee favoured the estimate of £58,223 per QALY gained

Table 1 (continued)

Number and ATMP name	ACI [TA 477]	ACI using chondrosphere [TA 508]	Autologous anti-CD19-transduced CD3+ cells [TA677]
Uncertainty	Evidence from five RCTs and one observational study. Lack of robust evidence to compare long-term effectiveness of ACI with microfracture, partially because of differences in the populations included in each trial. Lack of evidence on the relative benefits of different types of ACI, although clinicians' preferences vary. Lack of data to accurately estimate probability of requiring knee replacement surgery after failure of ACI. Uncertain cost at which ACI treatments would be made available to the NHS as discounts are confidential. Uncertainty about the modelled utility values for pts in whom ACI or microfracture is successful and unsuccessful, which means estimates about ICER vary widely. Uncertainty on how well utility values reflect the population considered for ACI in the NHS	Evidence from two RCT (phases II and III). Limited data on the long-term benefit of chondrosphere. Uncertainty about assumption that benefits of microfracture cease at 5 years, which likely underestimated ICERs. Despite uncertainty about comparison between chondrosphere and microfracture, other forms of ACI are not widely available in the NHS so cannot be considered as comparators	Uncertainty due to short follow-up and small number of pts in ongoing, phase III, multicentre, open-label, single-arm study. Lack of evidence comparing autologous anti-CD19-transduced CD3+ cells directly with the most common alternative treatment. Immature survival data mean that long-term survival and potential cure remain uncertain. Cost effectiveness very sensitive to age when treatment starts, and NHS pts are older than those included in the trial. Uncertainty about whether HRQoL among long-term survivors is comparable to general population of same age and sex
Discounting	3.5% for both costs and benefits as per reference case	3.5% for both costs and benefits as per reference case	3.5% for both costs and benefits
Subgroups	ACI likely to be cost effective only in subgroups of pts: -Pts who have not had previous knee repair -Pts who have minimal osteoarthritic damage to the knee -Pts with articular cartilage defects of > 2 cm <sup>2</sup>	ACI likely to be cost effective only in subgroups of pts (as per TA477): -Pts who have not had previous knee repair -Pts who have minimal osteoarthritic damage to the knee -Pts with articular cartilage defects of > 2 cm <sup>2</sup>	No comment
Additional benefits	Not considered	There is an unmet need because currently ACI is not widely available in the NHS, and there are no good alternative surgical options for people with defects > 2 cm <sup>2</sup>	No comment
Generalisability to NHS	Uncertainty whether utility values reported by trials reflected those of NHS pts	Findings from trials likely generalisable to the NHS	Evidence is generalisable to pts in the NHS (after pt selection)
Innovation	ACI, although not new, is technically innovative. However, innovation in this case did not bring benefit for pts beyond what was captured within the modelling	Chondrosphere is innovative, but the health benefits are already captured within the economic modelling	Innovative treatment, but reference case still applicable
Service reformulation/change in practice	ACI is only recommended in tertiary referral centres as the laboratory that makes the only licensed ACI technology available at the time of TA477 is affiliated with a tertiary referral NHS orthopaedic hospital	No comment, but acknowledgement that chondrosphere can be delivered by other centres besides tertiary referral centres as for TA477	No comment



Table 1 (continued)

Number and ATMP name	ACI [TA 477]	ACI using chondrosphere [TA 508]	Autologous anti-CD19-transduced CD3+ cells [TA677]
Inequalities	Inequalities could arise from excluding pts with severe arthritis of the knee (which is a formal contraindication in the marketing authorisation), but those were mitigated by allowing clinicians to assess suitability for ACI based on severity of osteoarthritis	Inequalities could arise from excluding pts with severe arthritis of the knee (which is a formal contraindication in the marketing authorisation), but those were mitigated by allowing clinicians to assess suitability for ACI based on severity of osteoarthritis	No comment
PAS	No comment, but mention that discounted prices may be available to the NHS	No comment	Early estimates suggest treatment could be cost effective, and collecting further data on PFS, OS and age when treatment starts will reduce uncertainty in the evidence. Therefore, autologous anti-CD19-transduced CD3+ cells are recommended for use as an option within the CDF. Company has a commercial arrangement (simple discount PAS and a managed access agreement including a commercial access agreement). This makes autologous anti-CD19-transduced CD3+ cells available to the NHS with a discount, but size is commercial in confidence
End of life	Not applicable	Not applicable	Autologous anti-CD19-transduced CD3+ cells meet the criteria to be considered a life-extending treatment at the end of life because pts receiving it are likely to live for < 24 months, and it could extend their life by at least 3 months
Number and ATMP name	Strimvelis [HST 7]	Voretigene neparvovec [HST 11]	Onasemnogene abeparvovec [HST 15]
Conditions	ADA-SCID	Inherited retinal dystrophies caused by <i>RPE65</i> gene mutations	SMA

Table 1 (continued)

Number and ATMP name	Strimvelis [HST 7]	Voretigene neparvovec [HST 11]	Onasemnogene abeparvovec [HST 15]
Recommendation	Strimvelis is recommended, within its marketing authorisation, as an option for treating ADA-SCID when no suitable HLA-matched related stem cell donor is available	Voretigene neparvovec is recommended, within its marketing authorisation, as an option for treating RPE65-mediated inherited retinal dystrophies in pts with vision loss caused by inherited retinal dystrophy from confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells. It is recommended only if the company provides voretigene neparvovec according to the commercial arrangement	Onasemnogene abeparvovec is recommended as an option for treating 5q SMA with a biallelic mutation in the <i>SMN1</i> gene and a clinical diagnosis of type 1 SMA in babies, only if: They are aged ≤6 months, or They are aged 7–12 months, and their treatment is agreed by the national multidisciplinary team. It is only recommended for these groups if: Permanent ventilation for > 16 h/day or a tracheostomy is not needed The company provides it according to the commercial arrangement. For babies aged 7–12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them ≥70% chance of being able to sit independently. Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a biallelic mutation in the <i>SMN1</i> gene and up to three copies of the <i>SMN2</i> gene in babies. It is recommended only if the conditions in the managed access agreement are followed
Type of AMT	Ex vivo gene therapy	Adeno-associated virus vector-based gene therapy	Adeno-associated virus vector-based gene therapy
Administration and cost	Single-dose treatment and lifelong effect. The price is €594,000 (excluding VAT; at an exchange rate of €1 to £0.85, this equates to £505,000)	Single dose. £613,410 per patient (excluding VAT)	Single dose. £1,795,000 (excluding VAT)
Clinical effectiveness	Strimvelis improves OS vs. HSCT. Severe infection rate is likely to be similar for Strimvelis and HSCT. Neither Strimvelis nor HSCTs improve the non-immunological aspects of ADA-SCID, and a substantial proportion of pts who have successful treatment will have lifelong impairments. Strimvelis treatment is expected to cause fewer AEs than other options during treatment because of the lower busulfan conditioning needed; there is also no risk of graft vs. host disease. The risk of cancer, although probably small, cannot be excluded and requires surveillance	Voretigene neparvovec has considerable benefit in terms of improving vision and preventing vision deterioration and disease progression. There is a biological rationale for treatment effect to be maintained	Onasemnogene abeparvovec provides important health benefits for babies aged ≤6 months with type 1 SMA. There is little evidence in babies who have treatment when they are aged >6 months. Onasemnogene abeparvovec is likely to result in better outcomes if treatment is given early, particularly before the onset of symptoms. Onasemnogene abeparvovec is likely to have long-term health benefits, but the extent of benefit is uncertain

Table 1 (continued)

Number and ATMP name	Strimvelis [HST 7]	Voretigene neparovvec [HST 11]	Onasemnogene abeparvovec [HST 15]
Cost effectiveness (ICER)	£91,910 and £84,172 per QALY vs. an HSCT from an HLA-matched unrelated donor and a haploidentical donor, respectively, at 3.5%. £54,072 and £49,429 per QALY vs. an HSCT from an HLA-matched unrelated donor and a haploidentical donor, respectively, at 1.5%	£114,956–155,750 per QALY gained at 3.5% discount rate. £60,908–86,118 per QALY gained at 1.5% discount rate	ICER not provided
Uncertainty	Rare disease, so small number of pts included in studies. Several RCTs; the first started 15 years ago. Lack of disease-specific HRQoL from randomised trials. Long-term survival after an HSCT or Strimvelis is highly uncertain but is one of the most influential factors affecting model results. Uncertain duration of need for bridging treatment with polyethylene glycol-modified adenosine deaminase and associated costs. Actual impact on NHS budget depends on number of pts, which is expected to be one to two per year. Treatment can only be delivered in one centre in Italy, so costs will be incurred for hospitalisation, accommodation and travel. This adds substantial uncertainty as it is unclear how payments will be made in Euros because of the fluctuating foreign exchange rate and how additional costs incurred by a pt during their stay (e.g., if hospitalisation is extended) will be covered	Small study (phase I) with 7.5 years' follow-up and small RCT (phase III) with 3–4 years' follow-up. Treatment effect is expected to last for decades but limited follow-up available, so duration of treatment effect is uncertain; assumption of 40-year treatment effect considered reasonable. No data on disease-specific HRQoL. Long-term effects and utility values were key uncertainties in economic model. Impact on budget largely depends on number of eligible pts, which was estimated by the company as 86 pts in England	Evidence from two completed and three ongoing open-label single-arm studies, with small sample size (13–33 babies). Short follow-up of 18–24 months means effect on long-term survival is unknown, and it is unclear whether long motor milestones that are achieved are maintained. Supportive care considered the most suitable comparator, but natural history studies have many limitations, and outcomes may not be comparable. Immature data introduced uncertainty in economic models, which were based on assumptions rather than actual outcomes (e.g., extrapolation of long-term effects). No data on disease-specific HRQoL from drug trials, so health-state utilities add uncertainty to the economic model. Uncertainties around the level of care needed in the long term, with the possibility that it may increase over a lifetime horizon. Uncertainties on the subsequent effect on carers' HRQoL
QALY weighting	QALY gain of 14.0 and 19.6 for Strimvelis vs. HSCT from an HLA-matched donor and a haploidentical donor. QALY weighting of 1.40 and 1.96 was applied, respectively	QALY gain was 12.1–17.7, so weighting of 1.2 was applied	QALY gain was 18.62 in the scenario considered most plausible, but a weighting of 1.86, which is lower than could be allowed for QALY gain, was applied due to substantial uncertainty
Discounting	Both discount rates (1.5 and 3.5%) should be considered because of uncertainty about whether pts treated with Strimvelis would be considered to have “normal or near-normal health” and whether the long-term benefits of treatment would be achieved because of the limited evidence	A 3.5% discount rate was deemed preferable because of the uncertainty about whether voretigene neparovvec fully met the criteria for using a discount rate of 1.5%. It was highly uncertain whether pts receiving voretigene neparovvec would be considered to have “normal or near-normal health” and whether the long-term benefits of treatment would be achieved	Onasemnogene abeparvovec was considered to meet the criteria for using a 1.5% discount rate despite uncertainty about long-term benefits and achievement of normal or near-normal health
Subgroups	No comment	Whether treatment varies across inherited retinal dystrophies caused by different <i>RPE65</i> gene mutations is uncertain but not biologically plausible	Treatment recommendations vary for different subgroups according to genetic mutations and type of SMA

Table 1 (continued)

Number and ATMP name	Strimvelis [HST 7]	Voretigene neparvovec [HST 11]	Onasemnogene abeparvovec [HST 15]
Additional benefits	Improvements to carer-related quality of life. There would be cost savings and benefits with Strimvelis incurred outside the NHS and personal and social services. No major changes in staffing and infrastructure would be needed	With sustained vision, children would be able to attend mainstream school, retain their independence, take part in social activities and achieve their full potential. Voretigene neparvovec would reduce financial impact on families as parents would not need to give up work to provide care and pay for expensive home adaptations. Voretigene neparvovec would decrease the expenditure incurred by non-NHS government departments that provide support for families affected by vision loss	Significant improvement in the quality of life of pts with SMA and their carers by achieving motor milestones such as sitting and walking, enabling participation in society and school. Even small gains in motor function, such as ability to roll from side to side, hold the head or lift the arms can translate into greatly improved quality of life for pts and carers
Generalisability to NHS	The age of the population who would receive Strimvelis in clinical practice may be lower than that in the clinical trial, which may lead to greater clinical benefit	Relevance of study results to clinical practice is difficult to predict in pts with less severe diagnoses because of individual variability	Evidence is generalisable to the NHS as earlier diagnosis is becoming more common
Innovation	Innovative technology, but no comment about whether reference case should be adjusted	Innovative technology, but no comment about whether reference case should be adjusted	Innovative technology, but no comment about whether reference case should be adjusted
Service reformulation/change in practice	People would need to travel to Italy for treatment with Strimvelis, so no additional infrastructure or staff training would be needed at specialist centres in England	Not specifically addressed but mention the need for staff training to reduce risk of AEs. It is feasible to implement this technology in NHS clinical practice	Onasemnogene abeparvovec would only be delivered in a small number of highly specialised centres because there is a need to concentrate expertise. This means families may need to travel long distances. Additional staff training may be required
Inequalities	Potential to reduce inequalities in waiting time for transplant related to lack of donors for certain ethnicities in whom ADA-SCID is more common (Irish traveller and Somalian family origins)	No issues	Possible delay in diagnosis in disadvantaged communities led the committee to allow treatment to be offered beyond 6 months in certain circumstances
PAS	No comment	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence
End of life	Not applicable	Not applicable	Not applicable
Number and ATMP name	OTL-200 [ID1666]	Betibeglogene autotemcel [ID968]	
Conditions	Metachromatic leukodystrophy	TDT	

Table 1 (continued)

Number and ATMP name	OTL-200 [ID1666]	Betibeglogene autotemcel [ID968]
Recommendation	<p>OTL-200 is not recommended, within its marketing authorisation, for treating metachromatic leukodystrophy characterised by biallelic mutations in the ARSA gene that reduce ARSA enzyme activity in children who have:</p> <ul style="list-style-type: none"> <li>Late infantile or early juvenile types, with no clinical signs or symptoms</li> <li>The early juvenile type, with early clinical signs or symptoms, and who can still walk independently and have no cognitive decline.</li> </ul> <p>This recommendation is not intended to affect treatment with OTL-200 that was started in the NHS before this guidance was published. Children having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person or their parents or carers</p>	<p>Betibeglogene autotemcel is not recommended, within its marketing authorisation, for treating TDT in pts aged <math>\geq 12</math> years who do not have a beta<sup>0</sup>/beta genotype, when HSCT is appropriate, but an HL/A-matched related HSC donor is not available</p>
Type of AMT	Gene therapy medicinal product that expresses the human ARSA gene (ex vivo genetically modified autologous CD34+ haematopoietic stem and progenitor cells)	$\beta$ -globin gene therapy for sickle cell anaemia and $\beta$ -thalassaemia, using a lentiviral gene delivery system
Administration and cost	Single dose. List price is £2,875,000 (excluding VAT; company submission). Company has a commercial arrangement, which would apply if the technology were recommended	Cost of betibeglogene autotemcel 1.2 to $20 \times 10^6$ cells/mL dispersion for a one-time infusion is £1,450,000 per pt (list price, excluding VAT). Company has a commercial arrangement, which would have applied if the technology had been recommended
Clinical effectiveness	Clinical effectiveness is highly unclear due to lack of consensual response criteria. Less than 50% of patients expected to have a full response	Modest evidence suggests that some pts either eventually no longer need blood transfusions or need them less often
Cost effectiveness (ICER)	ICER is commercial in confidence but outside the range NICE normally considers to be a cost-effective use of NHS resources (£100,000 per QALY)	The most plausible ICER was considerably higher than £30,000 per QALY gained

Table 1 (continued)

Number and ATMP name	OTL-200 [ID1666]	Betibeglogene autotemcel [ID968]
Uncertainty	<p>Non-randomised, open-label, prospective, single-centre trials with small sample size (25 pts in total). Clinical outcomes related to motor and cognitive function may not adequately reflect quality of life. OTL-200 could be effective for a pt's lifetime because the progeny of the infused cells maintains the gene correction. However, successful engraftment and migration of cells into the central nervous system could take up to 2 years, so the disease could progress before there is a treatment effect. Uncertainty as to whether pts included in analyses are generalisable to the population of eligible pts. Uncertainty about fresh and cryopreserved formulations of OTL-200, as the latter would be used commercially but evidence was from fresh formulation. Uncertainty about rate of progression and stabilisation of treatment response. No HRQoL data collected as part of the trials. Pooled ICER weighted by prevalence of different subgroups adds uncertainty because some subgroups have worse outcomes, the distribution of subgroups is unknown, there are very few pts in each subgroup and the ICER is very sensitive to distribution of subgroups</p>	<p>Uncertainty about life expectancy of pts with TDT due to recent improvements in treatment. Clinical efficacy based on three small, multicentre, single-arm studies (24 pts in total), with limited follow-up (5 years). Long-term follow-up study is ongoing. HRQoL based on UK Chart Review population as trial data were insufficient</p>
QALY weighting	QALY gain commercial in confidence. QALY weight between 1 and 3, but the exact weighting was uncertain and depended on the distribution of subgroups if pooled	Not applicable
Discounting	3.5% for both costs and benefits due to uncertainty about long-term effect and restoration of normal or near-normal health	3.5% for both costs and benefits due to uncertainty about long-term effect and life expectancy associated with TDT
Subgroups	Single ICER was presented weighted by prevalence of different subgroups	Only indicated for pts without beta <sup>0</sup> /beta <sup>0</sup> genotype
Additional benefits	Full effect of benefits beyond direct health benefits not completely quantified but considered qualitatively by committee. Benefits for children and their families	No comment
Generalisability to NHS	No comment	No comment
Innovation	Innovative treatment that can be life transforming, and full benefits not captured by economic model	Innovative treatment so an ICER closer to £30,000 per QALY gained was considered acceptable
Service reformulation/change in practice	No comment	No comment

Table 1 (continued)

Number and ATMP name	OTL-200 [ID1666]	Betibeglogene autotemcel [ID968]
Inequalities	Marketing authorisation states that pts should have treatment “before the onset of cognitive decline,” so it is critical to ensure that those with pre-existing learning disabilities are not disadvantaged in accessing the technology. Delayed diagnosis in children from disadvantaged groups may also create inequalities	Incidence of a condition in different population groups is outside the remit of a technology appraisal. In the UK, TDT is mostly seen in ethnic minority populations, the largest groups being in people with Pakistani, Indian or Bangladeshi family backgrounds
PAS	Company agreed a PAS with the Department of Health, but the level of the discount is commercial in confidence	Early estimates suggest treatment could be cost effective, and collecting further data on PFS, OS and age when treatment starts will reduce the uncertainty in the evidence. Therefore, autologous anti-CD19-transduced CD3+ cells are recommended for use as an option within the CDF. Company has a commercial arrangement (simple discount PAS and a managed access agreement including a commercial access agreement). This makes autologous anti-CD19-transduced CD3+ cells available to the NHS with a discount, but size is commercial in confidence. Betibeglogene autotemcel would be available to a wider age range than HSCT. However, it would only be accessible to a specific genotype
End of life	Not applicable	Betibeglogene autotemcel does not meet end-of-life criteria

*ACI* autologous chondrocyte implantation, *ADA-SCID* adenosine deaminase deficiency–severe combined immunodeficiency, *AE* adverse event, *AMT* advanced medicinal therapy, *ARSA* arylsulphatase A, *ATMP* advanced therapy medicinal product, *BSC* best supportive care, *BTk* Bruton’s tyrosine kinase, *CAR* chimeric antigen receptor, *CD* Crohn’s disease, *CDF* Cancer Drugs Fund, *EMA* European Medicines Agency, *HLA* human leukocyte antigen, *HRQoL* health-related quality of life, *HSC* homologous stem cell, *HST* homologous stem cell transplant, *HST* highly specialised technologies, *ICER* incremental cost-effectiveness ratio, *LSCD* limbal stem cell deficiency, *MHS* national health service, *NICE* National Institute for Health and Care Excellence, *OS* overall survival, *PAS* patient access scheme, *PFS* progression-free survival, *PFU* plaque-forming units, *PROs* patient-reported outcomes, *ptf(s)* patient(s), *QALY* quality-adjusted life-year, *RCT* randomised controlled trial, *SMA* spinal muscular atrophy, *TA* technology appraisal, *TDT* transfusion-dependent  $\beta$ -thalassaemia, *VAT* value-added tax

quality-adjusted life-year (QALY) threshold usually considered by NICE, whereas the ATMPs with ICERs of £30,000–50,000 were recommended for the CDF. For the three ATMPs approved under the highly specialised technologies guidance [5], which applies a threshold of £100,000 per QALY, the ICERs for strimvelis were under the threshold irrespective of discount rate, but those for voretigene neparvovec were over the threshold when a 3.5% discount rate was applied. In the case of onasemnogene abeparvovec, using a discount rate of 1.5%, the ICER was under the weighted threshold of £186,000 per QALY.

Technology appraisals also considered whether there were externalities or additional benefits beyond those captured by QALYs. These additional benefits for individuals included avoidance of negative impact of alternative treatments (holoclar) and improved independence, social participation and ability to achieve full potential (strimvelis, voretigene neparvovec and onasemnogene abeparvovec). Positive externalities were taken into account qualitatively in the recommendations made for highly specialised technologies, such as reduced financial impact on families and society overall due to cost savings for the NHS and non-NHS government departments (e.g., social care). Chimeric antigen receptor (CAR) T-cell therapies were deemed to have no additional benefits, whereas the appraisals of darvadstrocel, betibeglogene autotemcel and ACIs did not comment on additional effects and externalities.

## 4 Discussion

This review suggests that appraisals of ATMPs present specific, and arguably greater, challenges to NICE committees than do other technologies. Uncertainty pervades clinical and cost effectiveness in all appraisals because of the sparse or even absent evidence on utility values, long-term effects and costs of treatment versus comparators. These issues are partly due to the nature of the conditions, which are typically rare and severe, and partly due to the technologies, which are novel and yet to be fully understood. We explore the key issues related to the evaluation of clinical and cost effectiveness of ATMPs, and we discuss the potential implications of adoption of ATMPs for the NHS and society overall.

### 4.1 Clinical effectiveness

Overall, evidence on the clinical effectiveness of ATMPs was limited and weak, but this varied substantially across technologies. The main difficulty in determining the clinical effectiveness of ATMPs was related to the limitations of the studies available, which were mostly single-armed, non-blinded studies with small sample sizes and short follow-up. The poor quality of the studies available may be

because ATMPs are typically prescribed as end-of-line treatment to people with rare diseases, which limits sample size. However, this does not necessarily explain why studies were non-blinded and single-armed, which raises concerns about the pharmaceutical industry sponsoring those studies. The limited evidence available raised important issues for assessing clinical effectiveness. First, short follow-up meant that survival data were immature, so the survival estimates and overall duration of effects were highly uncertain. In this context, scenario analyses exploring the effects of different assumptions about long-term benefits might be advantageous, as shown by their use for the evaluation of onasemnogene abeparvovec [4]. Second, single-arm studies did not provide direct evidence of efficacy against comparators, and finding suitable comparator(s) with valid and reliable data available was difficult. For instance, data from previous studies often did not reflect contemporary practice because of the fast evolution of therapeutics, or they included populations with different disease stages and prognoses. Comparison with historical cohorts that studied the natural progression of disease was also naïve (e.g., OTL-200). This rendered quantification of benefits and potential harms associated with different treatment modalities challenging, which translated into uncertainty in the evaluation of clinical effectiveness.

The criteria for life-extending end-of-life treatments, which include (1) life-extending treatments for people with a short life expectancy (normally < 24 months) and (2) providing a gain in overall survival of > 3 months [5], were introduced to allow the QALYs gained by treatments that improve patient survival in terminal stages of disease to be valued more highly. Although these criteria have allowed approval of drugs that would have otherwise been denied to NHS patients, all but one have been cancer drugs [23]. In keeping with this, of the ATMPs, only three of the CAR T-cell therapies (TA559, TA567 and TA677) met the criteria for life-extending end-of-life treatment. Perhaps acknowledging the limited scope and questionable fairness of the end-of-life criteria, NICE is considering replacing these criteria by a modifier for severity of disease [4]. The actual number of technologies that will benefit from a severity modifier depends on how it is defined and applied, but they can be expected to form a broader range of conditions and to reflect more accurately societal values than the previous end-of-life criteria.

NICE has statutory and ethical duties to support innovative technologies, so greater risks may be accepted to enable access to highly innovative technologies, which have valuable benefits for patients and society [24]. Although NICE defines which technologies qualify as innovative [5], there is much room for interpretation, and ambiguity has resulted in significant variability in implementation [25]. This raises concerns as to whether innovation, which is not an independent social value, may be jeopardising the core values



of health and equity in the NHS [26]. The possibility of considering innovation as a modifier also does not garner NICE support at present, as there is no evidence that society values health benefits from innovative technology more than equivalent benefits from less innovative technology [27]. In keeping with this, no adjustment to the reference case was warranted for any of the ATMPs, despite all being considered highly innovative.

## 4.2 Cost Effectiveness

Overall, there was substantial uncertainty in estimates of cost effectiveness of ATMPs because of the lack of valid and reliable data to inform the economic models. This was reflected in the disagreements about model parameters between committees, evidence review groups and companies. The poor quality of the clinical studies was further compounded by a lack of data on patient-reported outcomes, particularly health-related quality of life. This meant that utility values specific to the condition of interest were often missing, and extrapolation from the literature introduced further uncertainty to the models (e.g., holoclax, strimvelis, voretigene neparvovec, betibeglogene autotemcel, onasemnogene abeparvovec, OTL-200). In some cases, economic models may have overestimated utility gains of treatment (e.g., talimogene laherparepvec, betibeglogene autotemcel). For CAR T-cell therapies, overestimation of long-term survival and cure points may have exerted a paramount effect on cost effectiveness, as those were key determinants of the economic models. In addition, QALY valuation when effects are predicted to be lifelong remains complex because of concerns about whether different social values apply to evaluations of potential cures and substantial uncertainty in long-term outcomes [28]. Nonetheless, the lifelong nature of the effects of strimvelis, voretigene neparvovec, onasemnogene abeparvovec and OTL-200 was assumed based on biological plausibility, and QALYs were weighted (i.e., granted an increased value) to reflect the added value of large QALY gains throughout life, thus enhancing their cost effectiveness. However, this is controversial as there is no evidence that society places additional value on technologies that are potentially curative, and NICE is not supportive of a specific modifier for potentially curative treatments at present [4].

NICE guidance recommends using a 3.5% discount rate for both costs and benefits, but a 1.5% discount rate is allowed when appraising treatments that “restore people who would otherwise die or have severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)” [7]. Although companies claimed that their products were eligible for the 1.5% discount rate (e.g., tisagenlecleucel, holoclax, betibeglogene autotemcel and OTL-200), committees noted that “it is rarely considered appropriate to change the discount rate”

and preferred the 3.5% discount rate in most cases. However, for strimvelis and voretigene neparvovec, committees stated that both discount rates would be taken into consideration, acknowledging the uncertainty about whether those therapies would restore normal or near-normal health. For onasemnogene abeparvovec, a 1.5% discount was applied, despite, arguably, similar uncertainty about whether effects would be sustained in the long term and patients would achieve normal or near-normal health. This suggests that a lower threshold for considering the 1.5% discount rate may be applied in highly specialised technology appraisals than in standard technology appraisals. The common disagreement between companies and committees on discounting demonstrates the subjectivity involved in the interpretation of the fulfilment of the eligibility criteria. Furthermore, concerns have been raised that the non-reference case discount rate is rarely applied as it sets a high bar for the technologies it otherwise appears to support by requiring no significant irrecoverable costs and implying that a high degree of certainty is needed [29]. For all these reasons, NICE is considering a proposal to use a reference case discount rate of 1.5% per year for both costs and health effects [4], which is the discount rate for health values recommended by the government [30]. Lowering the reference case discount rate may increase the cost effectiveness of ATMPs, particularly those that have high upfront costs and long-term health benefits.

ATMPs are, in general, very expensive, and patient access schemes have been used to lower the ICER and thus facilitate NICE approval [31]. These are agreements between the Department of Health and pharmaceutical companies that enable companies to offer discounts or rebates that reduce the cost of a drug for the NHS. Simple discount schemes have been preferred over complex schemes, such as provision of free stock, dose caps or payments by results (i.e., performance or outcome-based schemes) [32]. It is arguable, though, that the latter could be appropriate to ATMPs, when there is substantial uncertainty on long-term effects and high upfront costs [33]. National discounts are known to NICE committees, and cost-effectiveness models are based on discounted prices. However, “companies sometimes provide confidential [local] discounts to the NHS, making the real cost of cells difficult to ascertain” (TA477), in which case committees accept models based on the approximate list price for the technology. In addition, the exact details of discounts are commercial in confidence, which, albeit understandable, compromises transparency and may undermine patients’ trust in how decisions are made about rationing of healthcare resources in the NHS [34]. On the other hand, patient access schemes may be disproportionately benefitting certain technologies. CAR T-cell therapies were recommended for inclusion in the CDF, which allows their use in the NHS while further data are collected to support a robust appraisal of their cost effectiveness and a subsequent

final recommendation. It is arguable whether similar funding arrangements should be potentially available to all technologies irrespective of the underlying disease (e.g., darvadstrocel could have been approved under such a scheme whilst further data were being collected by a large trial). The 2019 general election featured a promise to replace the CDF with an Innovative Medicines Fund, but this is yet to be implemented.

The four ATMPs evaluated as highly specialised technologies listed children, and specifically very young children, as the primary beneficiaries. In these cases, the higher valuation of QALYs assigned to treatments that have potentially lifelong effects (implemented via a higher cost-effectiveness threshold) captured the increase in benefit that would result from delivering a potentially transformative treatment to children while remaining in line with NICE's view that a modifier based on age is not appropriate [4]. As ATMPs are expected to target severe genetic diseases that manifest in infancy, the valuation and measurement of QALYs in children presents substantial challenges. NICE recommends using a generic measure with good psychometric performance in the relevant age group and reporting who has completed the questionnaire [5]. Nevertheless, the difficulty of valuing and measuring utility in children introduces additional uncertainty to cost-effectiveness evaluations, and further research is warranted to refine methods for assessing health-related quality of life in children [35].

Subgroup analysis may be especially important for ATMPs, as ICERs are typically high and may vary significantly across subgroups. NICE allows committees to recommend treatment for a selected subgroup of patients irrespective of whether the technology is found to be clinically and cost effective for the whole population, provided that the decision is ethically and methodologically sound [5]. Although ten of the 14 technologies analysed in this review considered whether treatment effects would be different in certain subgroups of patients, only six made specific subgroup recommendations (talimogene laherparepvec, holoclar, ACIs, onasemnogene abeparvovec and betibeglogene autotemcel). The remaining three evaluations considered that data were lacking to determine whether there were meaningful differences in treatment effects across subgroups (tisagenlecleucel, voretigene neparvovec) or that it was clinically difficult to identify those subgroups (tisagenlecleucel). This clearly illustrates the challenges in assessing the credibility and relevance of differences between subgroups, which have also been acknowledged by NICE [4].

The impact on inequalities may be particularly relevant for the evaluation of innovative technologies, such as ATMPs, as there may be a greater risk of creating or exacerbating inequalities [36]. In this review, all ATMPs except strimvelis, ACI and onasemnogene abeparvovec were considered to have a neutral effect on inequalities.

The first could reduce inequalities in waiting time for transplant that result from a lack of suitable donors for certain ethnicities in whom the condition for which it is recommended (i.e., adenosine deaminase deficiency–severe combined immunodeficiency) is more common, such as Irish traveller and Somalian family origins. This then leads to increased waiting times and potentially worse outcomes for those individuals. Conversely, ACI could result in inequalities as marketing authorisation excludes those with severe osteoarthritis. However, this was mitigated by allowing clinicians to assess patients' suitability for ACI based on severity of osteoarthritis. In addition, restricting ACI in TA477 to tertiary referral centres may lead to geographical inequalities as ACI may not be widely available across the country. For onasemnogene abeparvovec, the potential for a delayed diagnosis in disadvantaged children led the committee to allow treatment to be offered to children aged > 6 months in certain circumstances, despite scant evidence on clinical effectiveness beyond 6 months of age. NICE's commitment to addressing inequalities is illustrated by the fact that it considered adding impact on inequalities as a modifier to future health technology appraisals [4]. This is based on equality legislation [37] and evidence suggesting that the UK population prioritises seeking a fair distribution of health across society and is willing to trade-off less health overall if the health is generated in disadvantaged groups, particularly for socioeconomic disadvantage [38]. However, further work is needed to explore which sources of inequality to include, whether direct and indirect effects would be considered, and how and in which circumstances this could be implemented in health technology evaluations.

Although none of the ATMPs included in this review required major service redesign and staff training, ATMPs are by nature likely to have significant service delivery effects. NICE prefers that the full additional cost of introducing a technology is included in the evaluation. However, it concedes that some of the costs may be apportioned between other technologies, particularly when "high-cost medical devices have other uses beyond the evaluated indication (either now or in the future) or for technologies that need substantial service redesign to introduce them (which may affect other technologies or people not having treatment with a technology)" [4]. This flexibility to allow non-reference case analysis may be especially suitable for ATMPs, as costs may be shared by different stakeholders and technologies. In addition, ATMPs may be associated with additional costs that would not commonly be considered in other technology evaluations, such as costs associated with travelling to specialist centres abroad. For strimvelis, these costs were not incorporated in the economic model, and it was unclear how those costs would be covered in the long term. However, whether this should be included in economic models

to fully reflect the cost for the NHS is arguable, especially if, as expected, these issues become increasingly common.

### 4.3 Implications for the National Health Service and Society Overall

Although ATMPs offer potentially important benefits for patients, their families and society overall, their high upfront and often one-off costs can pose challenges related to affordability and implementation in the NHS [39]. Many of the mitigation measures are commercial in nature (e.g., patient access schemes) and not directly in the remit of NICE technology evaluations. However, NICE is accountable to the NHS, the government and the public it serves, and thus the wider implications of health technology evaluations of ATMPs for the NHS and society overall cannot be overlooked.

The first concern raised by the implementation of ATMPs by the NHS relates to the generalisability of research conducted elsewhere. This question, albeit shared with other technologies, is paramount for ATMPs because of the scant evidence available. Committees sought advice from clinical experts and complemented this with data from observational studies in England, whenever possible (e.g., darvadstrocel). Findings were considered generalisable to clinical practice in the NHS for axicabtagene ciloleucel, tisagenlecleucel in TA567 and ACI in TA508. However, in other cases, generalisability was questionable because outcomes for the comparator did not represent contemporary outcomes in the NHS (e.g., relapse rates were much higher for the comparator of darvadstrocel in the single trial available than rates reported in the NHS), the characteristics of the patients in the studies did not match those of typical NHS patients (tisagenlecleucel in TA554, darvadstrocel, holoclax, strimvelis) or heterogeneity in treatment effects was possible depending on individual variability (voretigene neparvovec).

Second, ATMPs are associated with a larger financial risk for the NHS than many other technologies [39]. They often have high upfront and, depending on contractual arrangements, potentially irrecoverable costs, yet the full benefits may take many years to accrue or may not be permanent. Furthermore, the high cost per patient means there is high volatility, which may be challenging to accommodate in annual budgets and increase financial risks if there is an unexpectedly high number of cases. The quintessential question is how much risk the NHS should incur and in which circumstances, as well as whether the risk should be shared by pharmaceutical companies (e.g., by using outcome-based contracts) [40]. NICE considers that greater risks could be accepted for “conditions for which it is recognised that evidence generation is complex and difficult, such as rare diseases, innovative technologies, technologies that provide large benefits”, all of which apply to ATMPs [4].

Nonetheless, whereas voretigene neparvovec, strimvelis and onasemnogene abeparvovec were recommended despite the scant evidence on long-term benefits, betibeglogene autotemcel was not recommended, at least partially because of “the potential to commit the NHS to irrecoverable costs”. This illustrates the difficult compromise between allowing flexibility for non-reference case analysis (e.g., by accepting greater risks) and allocating resources to maximise population health [41].

Third, ATMPs may have wider consequences for patients, their families and carers, the NHS and other governmental sectors and ultimately society at large. Those consequences are often beneficial and hence associated with positive utility (e.g., reduced burden for paid and unpaid carers). However, they can be associated with disutility, particularly when ATMPs extend life expectancy but with significant disability, leading to an increased need for caregiving over a lifetime horizon. For instance, for onasemnogene abeparvovec, caregiver disutility was not included in the model because it was difficult to quantify the disutility for carers and it would increase the ICER, which was considered “counter-intuitive”. In other ATMP evaluations, wider benefits contributed qualitatively to the appraisal of the evidence and the final recommendation, as they were hard to quantify or intangible (e.g., OTL-200). This is partly due to the lack of data on these benefits, as no studies had included them as outcomes. However, even if data were available, the reference case does not contemplate wider benefits that may be accrued because of treatment, particularly when these are non-health benefits (e.g., reduced need for social care) or when they fall on someone other than the person receiving treatment (e.g., parents and carers in general). NICE guidance acknowledges that “care delivered by the NHS could have other benefits that are considered socially valuable but are not directly related to health and are not easily captured in a cost per QALY analysis” [7]. Nonetheless, incorporating techniques “that consider the trade-off between health benefits and non-health benefits quantitatively” into decision making was considered unsuitable in 2013, and it did not feature in the case for change of health technology evaluation in 2020 [4]. NICE recommends that non-reference case analysis is used when there are substantial identifiable health benefits not captured by QALYs and emphasises the need to develop methods to formally incorporate qualitative evidence into decision making [4].

## 5 Conclusion

NICE evaluation of ATMPs revealed significant challenges, mainly related to large uncertainty about long-term and potentially curative effects, high upfront costs, discounting, innovation, benefits above and beyond QALYs and

apportioning of costs. However, these challenges are not unique to ATMPs, so completely different methods may not be required. Adaptations to the conventional decision-making process, such as the use of flexible non-reference case analysis, integration of different sources of evidence, and special funding arrangements, may improve appraisal of ATMPs.

## Declarations

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**Availability of data and material** All data are provided in the manuscript.

**Ethics approval** Not applicable.

**Consent** Not applicable.

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## References

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) No 726/2004. The Official Journal of the European Union 2007.
- Committee for Advanced Therapies. EMA warns against using unproven cell-based therapies EMA/CAT/94295/2020. Amsterdam: European Medicines Agency; 2020.
- Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess.* 2017;21(7):1–204.
- National Institute for Health and Care Excellence. Reviewing our methods for health technology evaluation: consultation. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice/chte-methods-consultation>. Cited 12 Dec 2020.
- National Institute for Health and Care Excellence. Guidance and advice list. <https://www.nice.org.uk/guidance/published?type=hst>. Cited 12 Dec 2020
- Summaries of scientific recommendations on classification of advanced therapy medicinal products. <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification/summaries-scientific-recommendations-classification-advanced-therapy-medicinal-products>. Cited 20 Dec 2020
- National Institute for Health and Care Excellence. Guide to the processes of technology appraisal. PMG19. England 2018.
- National Institute for Health and Care Excellence. Talimogene laherparepvec for treating unresectable metastatic melanoma. <https://www.nice.org.uk/guidance/ta410/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. <https://www.nice.org.uk/guidance/hst7/history>. Cited 6 Jul 2021
- National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. <https://www.nice.org.uk/guidance/ta554/history>. Cited 6 Jul 2021
- National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. <https://www.nice.org.uk/guidance/ta567/history>. Cited 6 Jul 2021
- National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. <https://www.nice.org.uk/guidance/ta559/history>. Cited 6 Jul 2021
- National Institute for Health and Care Excellence. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. <https://www.nice.org.uk/guidance/hst11/history>. Cited 6 Jul 2021
- National Institute for Health and Care Excellence. Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma. <https://www.nice.org.uk/guidance/ta677/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. <https://www.nice.org.uk/guidance/indevelopment/gid-ta10334>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Onasemnogene abeparvovec for treating spinal muscular atrophy. <https://www.nice.org.uk/guidance/hst15/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. OTL-200 for treating metachromatic leukodystrophy. <https://www.nice.org.uk/guidance/indevelopment/gid-hst10028/documents>. Cited 13 Jul 2021.
- National Institute for Health and Care Excellence. Holoclar for treating limbal stem cell deficiency after eye burns. <https://www.nice.org.uk/guidance/ta467/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Darvadstrocel for treating complex perianal fistulas in Crohn's disease. <https://www.nice.org.uk/guidance/ta556/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee. <https://www.nice.org.uk/guidance/ta477/history>. Cited 6 Jul 2021.
- National Institute for Health and Care Excellence. Autologous chondrocyte implantation using chondrosphere for treating

- symptomatic articular cartilage defects of the knee. <https://www.nice.org.uk/guidance/ta508/history>. Cited 6 Jul 2021.
22. Withdrawal of the marketing authorisation in the European Union EMA/303072/2015. London: European Medicines Agency; 2015. p. EMA/303072/2015.
  23. Macaulay R, Patel P. Applying Nice end of life criteria in the ERA of drug approvals based on single-ARM trial data. *Value Health*. 2017;20(9):A457.
  24. National Institute for Health and Care Excellence. Our principles. London.
  25. Charlton V, Rid A. Innovation as a value in healthcare priority-setting: the UK experience. *Soc Just Res*. 2019;32(2):208–38.
  26. Bryan S, Lee H, Mitton C. ‘Innovation’ in health care coverage decisions: all talk and no substance? *J Health Serv Res Policy*. 2013;18(1):57–60.
  27. Kennedy I. Appraising the value of innovation and other benefits: a short study for NICE. London: National Institute for Health and Care Excellence; 2009.
  28. Pearson SD, Ollendorf DA, Chapman RH. New cost-effectiveness methods to determine value-based prices for potential cures: what are the options? *Value Health*. 2019;22(6):656–60.
  29. O’Mahony JF, Paulden M. NICE’s selective application of differential discounting: ambiguous, inconsistent, and unjustified. *Value Health*. 2014;17(5):493–6.
  30. The Green Book: central government guidance on appraisal and evaluation London: HM Treasury. 2020.
  31. Seoane-Vazquez E, Shukla V, Rodriguez-Monguio R. Innovation and competition in advanced therapy medicinal products. *EMBO Mol Med*. 2019;11(3):e9992.
  32. Macaulay R, Jamali E. PHP218: nice patient access schemes— who, what, why, when and how. *Value Health*. 2015;18:A335–766.
  33. Towse A, Fenwick E. Uncertainty and cures: discontinuation, irreversibility, and outcomes-based payments: what is different about a one-off treatment? *Value Health*. 2019;22(6):677–83.
  34. Drummond M, Sorenson C. Nasty or nice? A perspective on the use of health technology assessment in the United Kingdom. *Value Health*. 2009;12(Suppl 2):S8–13.
  35. Ravens-Sieberer U, Erhart M, Wille N, Wetzel R, Nickel J, Bullinger M. Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. *Pharmacoeconomics*. 2006;24(12):1199–220.
  36. Weiss D, Rydland HT, Øversveen E, Jensen MR, Solhaug S, Krokstad S. Innovative technologies and social inequalities in health: a scoping review of the literature. *PLoS ONE*. 2018;13(4):e0195447.
  37. Equality Act. London: Parliament of the UK. 2010.
  38. McNamara S, Holmes J, Stevely AK, Tsuchiya A. How averse are the UK general public to inequalities in health between socioeconomic groups? A systematic review. *Eur J Health Econ*. 2020;21(2):275–85.
  39. Spoons J, Miners A, Cairns J, Palnoch D, Summerfield A, McEntee J, et al. Payer and implementation challenges with advanced therapy medicinal products (ATMPs). *BioDrugs*. 2021;35(1):1–5.
  40. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JMG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ*. 2019;20(3):427–38.
  41. Gonçalves E. Advanced therapy medicinal products: value judgement and ethical evaluation in health technology assessment. *Eur J Health Econ*. 2020;21(3):311–20.