MODELLING HEALTH-RELATED IMPACTS

The value of cell and gene therapies to the UK economy

CONTRACT RESEARCH REPORT
October 2025

Chris Sampson
Sukanya Subramaniyan
Matthew Napier
Hania El Banhawi
Panos Kefalas
Laura Beswick
Jacqueline Barry
Matthew Durdy
Grace Hampson

ohe.org

OHE

CATAPULT
Cell and Gene Therapy

OCTOBER 2025

MODELLING HEALTH-RELATED IMPACTS

The value of cell and gene therapies to the UK economy

Chris Sampson
Office of Health Economics, London

Sukanya Subramaniyan
Office of Health Economics, London

Matthew Napier
Office of Health Economics, London

Hania El Banhawi
Office of Health Economics, London

Panos Kefalas
Cell and Gene Therapy Catapult, London

Jacqueline Barry
Cell and Gene Therapy Catapult, London

Laura Beswick
Cell and Gene Therapy Catapult, London

Matthew Durdy
Cell and Gene Therapy Catapult, London

Grace Hampson
Office of Health Economics, London

Please cite this report as:
Sampson C., Subramaniyan S., Napier M., El Banhawi H., Kefalas P., Beswick L., Durdy M., Hampson G. 2025. The value of cell and gene therapies to the UK economy: Modelling health-related impacts. OHE Contract Research Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/value-of-cell-and-gene-therapies-to-the-uk-economy/

Corresponding Author:
Chris Sampson
csampson@ohe.org

About OHE contract research reports

Many of the studies OHE performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Contract Research Reports are subject to internal quality assurance and undergo external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views of OHE as an organisation.

Funding and acknowledgements

This Contract Research Report was commissioned and funded by the Cell and Gene Therapy Catapult, with support from Innovate UK.

Table of contents

Executive summary

Cell and gene therapies (CGTs) are moving rapidly from specialist trials to routine care: more than thirty products are already licensed worldwide and over two thousand are in clinical development. Their promise—a single intervention that can arrest or even cure previously intractable diseases—creates both opportunity and pressure for health systems.

The UK is well placed to capture the public value of a **CGT-driven system-shift**, realised through its existing life-science ecosystem and national health service. The objective of such a shift is to ensure that CGTs are routinely incorporated into care pathways and that the UK is established as a hub for research and manufacturing. Achieving this, however, requires decisions that go beyond the reimbursement of individual products: government and industry must coordinate investment in manufacturing capacity, clinical infrastructure, data systems, regulation, and workforce skills.

This report presents the first part of a **whole-system economic framework** designed to quantify the return on coordinated investment in cell and gene therapy. It considers the range of benefits resulting from health gains due to broader use of cell and gene therapies, including advantages for the health system and the wider economy (we refer to these as 'health-related benefits'). By valuing costs and benefits across patients, care systems, and the wider economy—and aligning the analysis with HM Treasury's Green Book—we offer an evidence base for academics, policymakers, and investors who must judge whether to invest in a CGT system-shift.

A new analytic approach

We adapt conventional approaches to decision analytic cost-effectiveness modelling, characterising value according to the level at which value is realised:

- **Individuals** captures patient and caregiver impacts, including health outcomes measured in quality-adjusted life years (QALYs) and personal financial impacts.
- **Systems** includes net NHS and social care costs, including downstream expenditure.
- **National economy** includes value associated with labour market participation, productivity, and informal care contributions.

The model is implemented as an open-source state transition template, populated with two evidence sets: Scenario A uses the most recent clinical and economic evidence relating to existing technologies; Scenario B explores an optimistic but plausible frontier. In contrast to individual technology assessments, the analysis accounts for current and future patient flows to identify value realised over a fixed period. A ten-year time horizon anchors the analysis to government spending review cycles, while an annual steady-state analysis provides estimates for long-term scaling. Four contrasting indications were selected to test the framework and provide an overview of the potential value of a system-shift in each area: acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), beta-thalassaemia (BT), and Alzheimer's disease (AD).

Main findings

Across the four case studies, widening CGT access yields large net societal benefits, even when only health-related outcomes are counted. Our findings demonstrate the substantial societal value of CGTs, derived from increased productivity, reduced absenteeism, and enhanced quality of life for patients and caregivers. CGTs are already in use in ALL, AML, and BT, and have small eligible populations. Despite small population sizes, we show significant potential for the realisation of value within a 10-year time horizon. For example, the value of CGTs to individuals with AML is £578 million, driven primarily by health gains. Meanwhile, the most significant value created in BT relates to healthcare cost savings, at around £74 million.

As shown in Table 1, under a conservative scenario (Scenario A), the additional value of widening access to CGTs is projected to create value between **£20-40 billion** across the four case study indications, depending on the category of value considered. AD dominates the aggregate because of its prevalence, but every indication is associated with significant returns in at least one category, even ALL, for which we modelled a small paediatric population.

Table 1 Summary of case study findings for the value of a CGT system-shift

		VALUE OF SYSTEM-SHIFT*			
INDICATION	**POPULATION SIZE**	**INDIVIDUALS**	**SYSTEMS**	**ECONOMY**	**MAIN DRIVER**
ALL	310	£11 m	£0.1 m	£0.6 m	Longer survival in a small cohort
AML	23,970	£583 m	£463 m	£5.5 m	Durable remission reducing care needs
BT	426	£52 m	£74 m	£51 m	Transfusion independence
AD	973,160	£39.6 bn	£19.9 bn	£21.5 bn	Slower progression, reduced care burden

** Estimates represent the incremental monetised value of outcomes over 10 years*

Implications

For policymakers, the results signal the scale of the prize and the potential cost of delay. By presenting benefits and costs on a common monetary scale, and separating to whom value accrues, the analysis can support top-level and cross-departmental business cases that must satisfy both health and industrial strategy objectives. The analysis may also inform payment and risk-sharing mechanisms to help align incentives between the Treasury and the NHS.

For industry, aggregate demand signals matter. Even under conservative assumptions, the ten-year returns on wider access to CGTs could be substantial and may help justify the location of advanced therapy manufacturing capacity in the UK.

For researchers, the framework offers a transparent, adaptable starting point for evaluating other treatment paradigm-shifting investments requiring system-level change and warranting consideration by diverse budget holders. The template model script is publicly available, allowing researchers to interrogate its assumptions, incorporate emerging data, and test alternative valuation methods.

Next steps

Our approach integrates the broad societal perspective recommended by the Green Book, applies it consistently across four heterogeneous diseases, and provides model code and inputs for scrutiny. Nevertheless, the current report focuses on benefits related to four indications only (benefits arising from a whole system shift would be much larger), and only describes benefits derived from health improvements. It excludes industrial spillovers and revenue factors that could materially increase the benefit-cost ratio. The type and scale of investment required to realise a CGT system-shift are also yet to be identified. Subsequent stages of work will address some of these questions.

Our work supports the view of a UK CGT system-shift as a definable investment option rather than an abstract aspiration. Even a conservative reading of the health-related gains makes a compelling public value case; the inclusion of industrial and knowledge economy effects is likely to strengthen it further. The framework offered here provides researchers and decision-makers with a flexible and open-source tool for turning bold ambitions into evidence-based action.

1 Introduction

Cell and gene therapies (CGTs) are advanced therapy medicinal products (ATMPs) with the potential to revolutionise the treatment of disease. Gene therapies work by modifying parts of a patient's DNA, through the insertion of 'recombinant' genes into the body (EMA, 2017). Gene therapies can prevent or correct the underlying genetic defects of genetic disorders, potentially offering substantial health gains for patients (Besley et al., 2022). Cell therapies involve the transfer of specific cell types that have been cultivated to contain genetic information to induce the intended therapeutic response. One example is chimeric antigen receptor (CAR) T-cell therapy. In this case, the process involves collecting T-cells, which are then altered to become CAR T-cells and then re-introduced into the bloodstream, where they recognise and attack cancer cells (CRUK, 2024).

Together, CGTs represent an opportunity to transform health outcomes and reach areas of current unmet need for many patients. They have the potential to offer significant value to patients, health and social care systems, and wider society, and to play a central role in a new era of advanced therapies, supporting a shift from chronic disease management to prevention of future healthcare needs.

However, there are barriers to wider uptake of CGTs in the UK, relating to manufacturing, infrastructure, regulation, value assessment, and delivery (Beswick, 2024). To support wider adoption of CGTs in the UK, piecemeal and technology-specific funding may be insufficient, and there is merit in considering a system-wide approach, in the form of a CGT system-shift.

A CGT SYSTEM-SHIFT

Such a CGT system-shift would be characterised by a broad acceptance of CGTs by healthcare payers and widespread implementation in the NHS. The UK would be a hub for research and development in innovative health technologies, in line with the NHS's 10-Year Health Plan's ambition for the UK to be in the 'driving seat' of innovation, fostering a highly skilled workforce, economic growth, and a healthier population (NHS, 2025b).

The system-shift is described in more detail in section 2.1.

Evaluative research in health economics has long embraced a healthcare decision-maker perspective (Sugden and Williams, 1978), whereby the evaluation focuses on health gains to the patient and costs (and savings) to the healthcare system. Indeed, a significant body of research has investigated the clinical and cost-effectiveness of cell and gene therapies using this perspective (Lloyd-Williams and Hughes, 2021; Petrou, 2023; Ho et al., 2021).

Yet, in recent years, researchers have embraced the notion of alternative decision-makers valuing outcomes beyond health (Walker et al., 2019). This is in part a recognition that health plays a role in determining an individual's productivity, earning potential, and economic contribution to society (Pinna Pintor, Fumagalli and Suhrcke, 2024; Bloom and Canning, 2003). There is compelling evidence that health significantly affects an individual's economic outcomes, resulting in higher employment rates and increased hours worked (Pinna Pintor, Fumagalli and Suhrcke, 2024). These benefits to the economy arise from the health improvements realised through effective healthcare, but may justify investment beyond the reimbursement of individual technologies and beyond healthcare in general.

In this report, a collaboration between the Office of Health Economics and the Cell and Gene Therapy Catapult, we outline a novel methodological approach for evaluating the economic impact of CGTs collectively. This is to inform the value of a 'CGT system-shift'. We apply our methodology to four case studies, representing disease areas, to provide initial estimates of the value of a CGT system-shift that occurs as a result of the health benefits (we refer to these as health-related benefits). These results will demonstrate the potential scale of the benefits that could be realised via the significant health improvements offered by CGTs to the UK. These analyses will form the foundation for further research. Future studies will seek to estimate value associated with wider (non-health-related) economic benefits and the costs involved with the system-shift, with a view to informing investment decision-making.

2 Rationale

This research aims to inform decision-making at the national government level. The Green Book (HM Treasury, 2022) is a guidance document published by HM Treasury, setting out best practices for the appraisal and evaluation of public policies and programmes. Decisions about public expenditure and investments should be informed by the framework outlined in the Green Book, according to which the first step in policy evaluation is to provide a strong rationale and need for the policy itself. This is the starting point for our analysis.

CGTs are distinct from many other types of treatment in their ability to address the root causes of disease, rather than managing symptoms. Unlike traditional pharmaceutical therapies, which may require lifelong administration, CGTs offer the potential for durable or even permanent therapeutic effects through a single intervention. A shift to CGTs thus represents a paradigm shift in treatment practice, from ongoing management to potential cures, which can drastically alter care pathways and delivery models across disease areas.

2.1 The system-shift

We seek to demonstrate the rationale for a 'system-shift', rather than a specific investment or policy change. By this, we refer to a strategic and coordinated transformation of a particular industry or sector of the economy. This may be achieved through deliberate policy interventions, targeted investment, and/or regulatory alignment. A 'system-shift' should be perceived as a change of the system, rather than a change within the system, with a reorientation of objectives and institutional frameworks and a view to achieving broad social objectives.

A system-shift, in this context, should be understood as a deliberate and coordinated reconfiguration of the health and life sciences ecosystem, to enable the routine integration of CGTs into clinical practice. This is not a marginal or incremental change, but a transformation that requires system-level investments across multiple domains: manufacturing infrastructure, regulatory frameworks, clinical delivery models, data systems, and workforce capabilities. Without such investments, the full potential of CGTs is not likely to be realised.

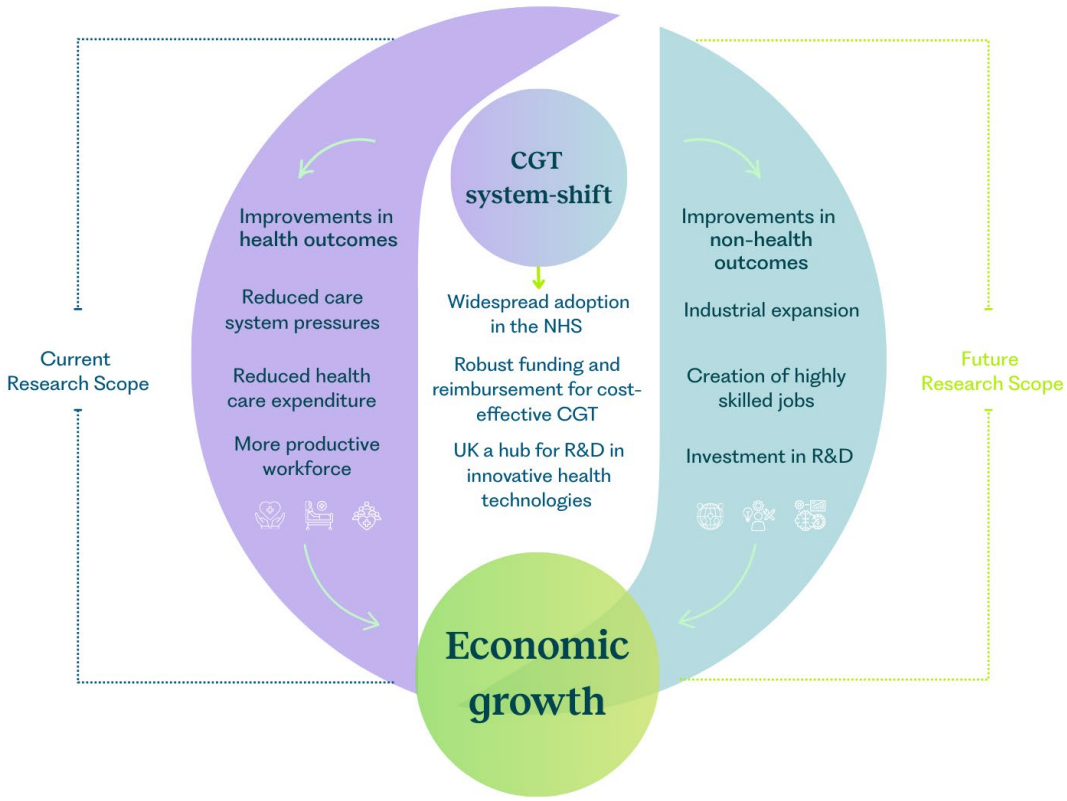
A system-shift is not only about enabling access to existing therapies; it is about reshaping the conditions under which innovation occurs and is adopted. As a result, we may see reductions in the cost of goods, as manufacturing processes mature and scale. We would also see expansion in the size of eligible populations, as earlier intervention becomes feasible and as clinical and regulatory systems become more accommodating. These changes could unlock substantial value across health and social care systems and the wider economy, realising the return on public and private investment.

The system-shift that we seek to evaluate is the establishment of the UK as a hub for research, development, and wider adoption of CGTs: a CGT system-shift. Of particular interest to this research is the necessity for a shift in how CGTs are evaluated, going beyond individual technologies and their health and health system benefits, towards viewing the value of CGT adoption at a system level.

A CGT system-shift in the UK would seek to secure the wider economic potential of CGTs including a healthier population, a highly productive workforce, and economic growth. Here, we describe the rationale for such a change in policy and practice. This is framed within a policy context defined in terms of the prevailing economic conditions in the UK, challenges faced by the NHS, and population health dynamics. We outline how a CGT

system-shift may lead to gains across relevant metrics, and consider the changes needed to achieve this. A simplified overview is given in Figure 1, which shows examples of health-related benefits (within the scope of this report) and improvements in non-health-related outcomes (beyond the scope of this report). Both health-related benefits and non-health outcomes are expected to influence economic growth.

Figure 1 Overview of rationale for CGT system-shift



2.2 Policy context
Poor economic growth

Economic growth in the UK, measured by real gross domestic product (GDP), has been historically slow since the 2007-09 financial crisis. Between 1993 and 2007, the economy grew by an average of 3% annually. This fell to 1.5% between 2009 and 2023 (Harari, 2024), to 1% between Q3 2023 and Q3 2024 (ONS, 2024d), and has further stagnated in recent months.

This lack of growth has been attributed to, among other factors, poor growth in labour productivity, as measured by economic output per hour worked. Recent data from the ONS in Q3 2024 has shown that labour productivity fell by 1.8% in the UK year on year compared to Q3 2023 (Romei and Smith, 2024). Economists have cited multiple factors driving low labour productivity in the UK, including low investment and policy uncertainty (Harari, 2024), but the definitive causes of the UK's 'productivity puzzle' remain uncertain.

Nevertheless, boosting productivity is essential for the realisation of long-term economic growth. Improvements in population health are likely to be an important driver of growth at the macroeconomic level (Sharma, 2018), as has been recognised by NHS leaders (Wood and Bosch, 2022). In part, this is likely to be driven by improvements in productivity at the individual level, through reductions in absenteeism and presenteeism (Koopmanschap, Burdorf and Lötters, 2013; Schultz, Chen and Edington, 2009).

Another lever to unlocking economic growth is to increase economic activity in the UK. Over 2.5 million people are out of work, defined as economically inactive, due to long-term sickness (ONS, 2023a). This represents an increase of over 400,000 since the beginning of the COVID-19 pandemic. The current Labour government in the UK has prioritised increasing economic activity, outlined in the white paper titled 'Get Britain Working' (Department for Work & Pensions, 2024). Supporting individuals with a long-term illness in returning to work is a key element of this strategy.

NHS in crisis

The current state of the UK NHS is an important contextual factor to consider. There are more than 100,000 vacancies across the NHS, despite the overall workforce growing by more than 30% in the last 15 years (Mallorie, 2024). Excess demand is putting NHS and social care staff under significant pressure.

A recent analysis by the Health Foundation forecast that the demand for healthcare will increase due to an ageing population and greater complexity in healthcare needs (Rocks et al., 2025). The average diagnosed illness rate in the population from 2019-2040 is expected to increase by 5.3% when excluding demographic changes in the population, and by almost 25% when population ageing is accounted for.

Moreover, by 2040, more than 9.1 million people are expected to be living with major illnesses in England, compared to approximately 6.6 million in 2019 (Watt et al., 2023). These expected trends in health and demography will place an increasing burden on already overburdened health and social care systems.

Barriers to CGT adoption

Greater capacity for the development and adoption of CGTs represents a potential mechanism for addressing this challenging policy context.

However, there are substantial barriers to accessing CGTs that necessitate broader system change (Sharma and John, 2024; Wagner et al., 2024). CGTs are considered disruptive technologies, posing challenges to health systems in terms of affordability, infrastructure, and delivery (Beswick, 2024; Wagner et al., 2024; Phares et al., 2024). The way that health systems currently pay for and deliver medicines is designed primarily around long-term treatments for chronic illnesses (Hampson, Towse and Zhang, 2021). Health systems are typically not well-designed for treatments like CGTs, which are often associated with single-administration and high upfront costs, delivering long-term and potentially curative outcomes (Henderson et al., 2025). This presents a significant affordability challenge when evaluated in line with current approaches to medicines reimbursement (Wong et al., 2023). There is also uncertainty in the long-term benefits of CGTs, which extend far beyond the time horizon of observational studies; this characteristic is used as a justification for coverage exclusions (Wagner et al., 2024). Uncertainty manifests at the individual patient level (in terms of the persistence of health benefits) and at the system level (in terms of the future value and economies of scale associated with wider use of CGTs).

2.3 Benefits

The anticipated benefits of achieving the CGT system-shift include improvements in population health, reductions in health and social care system pressures, and growth in the national economy. These benefits are particularly significant given the current context in which existing technologies are failing to meet many patients' needs or address health system challenges. Despite ongoing advances in drug development, much of the innovation pipeline continues to focus on incremental improvements rather than transformative change. As a result, many conditions remain poorly treated, and the burden on health and care services continues to grow.

In contrast, CGTs represent a fundamentally different class of innovation. They offer the potential for durable outcomes through a single intervention, disrupting the traditional model of chronic disease management. This shift has implications not only for clinical outcomes but also for how value is generated and distributed across the health and social care systems and the wider economy.

CGTs can reduce the need for long-term treatment, lower the incidence of complications, and alleviate the burden on caregivers and health services. Some CGTs help to reduce hospitalisations and long-term management of conditions (Firth et al., 2021; Wagner et al., 2024; Salzman et al., 2018), alleviating pressure on an overburdened NHS.

It's well-accepted that health plays a role in determining an individual's productivity, earning potential, and economic contribution to society (Pinna Pintor, Fumagalli and Suhrcke, 2024; Bloom and Canning, 2003). Health issues can lead to significant productivity losses in the form of presenteeism and absenteeism (Schultz and Edington, 2007; Asay, 2016). Presenteeism is the impact on productivity of working while ill, and absenteeism is the time taken off due to illness. It's been estimated that respiratory infections alone cost UK businesses £44 billion each year, due to absenteeism and presenteeism (Hayes et al., 2024).

There is evidence that individuals in better health have higher earning potential, improved labour supply, higher employment rates, and increased working hours (Pinna Pintor, Fumagalli and Suhrcke, 2024). Furthermore, this impact can be felt on informal caregivers, whose productivity could be impacted through time spent carrying out caregiving activities rather than work (Josten, Verbakel and Boer, 2022). The time spent caregiving also has a value in itself, and in the UK this is estimated to be approximately £184 billion (Carers UK, 2025), almost the equivalent of the entire NHS budget.

Improvements in health associated with access to CGTs are expected to lead to improved productivity and labour market outcomes for both patients and caregivers (Advanced Therapy Treatment Centres, 2022; Cell and Gene Therapy Catapult, 2023; Salzman et al., 2018).

The current analysis focuses on estimating the potential benefits associated with a system shift towards CGTs, including the examples provided in the upper half of Figure 1. As introduced in Figure 1, the rationale for investment extends to a broad range of benefits that may influence economic growth. The scope of this report is partial, limited to those benefits that are realised as a consequence of health improvements and their spillovers. Future work will extend the analysis to include improvements in non-health-related benefits, as introduced in the lower half of Figure 1. This includes industrial expansion, the creation of highly skilled jobs, and investment in research and development. For example, there is potential for the development of industrial capacity and market expansion to take advantage of a projected growth in the global gene therapy market to almost $100 billion by 2033 (Market Data Forecast ltd, 2025). Future analyses will support a more complete characterisation and quantification of the rationale for investing in a CGT system-shift, and the benefits that may be realised.

3 Our approach

The scope of our current analysis is the potential health-related economic value of access to CGTs in general. Our interest is not in estimating the value of specific technologies. In this way, our approach is complementary to health technology assessment (HTA) and is distinct from typical HTA methods.

3.1 Perspective

Our approach adopts a societal perspective, with the consideration and valuation of outcomes broadly aligned with Green Book recommendations (HM Treasury, 2022). We appraise CGTs in terms of their social (public) value, based on principles of welfare economics and social welfare efficiency. Social or public value includes all significant costs and benefits that affect the welfare and well-being of the population.

A narrower healthcare perspective typically assumes a fixed budget, and a decision-maker whose objective is to maximise health from that budget, only accounting for costs that fall on the budget deemed relevant (Brouwer and van Baal, 2023; Henderson et al., 2025). Some health technologies, particularly those of a transformative nature like ATMPs, may have a wider impact beyond costs to the health system and direct health benefits which may accrue over a longer time horizon (Henderson et al., 2025). Failing to fully account for these costs and benefits risks a sub-optimal allocation of resources (Wouterse et al., 2023). Shifting to a full consideration of the welfare impact of an intervention can help inform optimal decision-making (Brouwer and van Baal, 2023).

3.2 Analytical approach

Our analysis adopts principles of the Green Book, as described above. However, this report does not describe a full cost-benefit analysis. Our analysis is partial in several ways.

First, in developing the approach described in this report, we only apply our analysis to a selection of case studies, rather than a complete representation of the anticipated consequences of investing in a CGT system-shift. The purpose of the case studies is to illustrate our methodology and to provide signals of the magnitude of (health-related) value that may be realised from investment.

Second, we measure and value outcomes in a disaggregated way, to identify the level at which value is accrued. This does not align with typical (Green Book) approaches to cost-benefit analysis. In our analyses, value accrued at different levels should not be considered additive, because of a risk of double-counting. For example, the value that individuals attribute to their own health gains is partially determined by the increase in economic activity that it facilitates, which can also be captured as a value to the economy as a whole. A full cost-benefit analysis would demand a resolution to the challenge of double-counting.

Base case analysis

Our base case analysis adopts a 10-year time horizon, based on guidance from the Green Book. It is not anticipated that this time horizon will capture all value that may arise from a CGT system-shift. Rather, this time horizon is intended to align with significant government spending reviews and therefore, to provide an informative base case to decision-makers.

Steady-state analysis

In addition to the fixed time horizon base case analysis, we conduct a steady-state analysis. This analysis is intended to represent a long-run equilibrium in which the annual incidence of new patients is balanced by those who recover or die. In this scenario, the CGT system-shift has been realised and in place for many years and all implementation effects (e.g. learning curves, backlog clearance, one-off entry costs) have been cleared. Presenting these estimates is important given that, once a system-shift is realised, decision-makers will need to understand its annual implications.

Steady-state estimates can also provide a scalable estimate of the value of CGTs, disregarding the timing of benefits including delays in their realisation or any front-loaded cost associated with treating a prevalent population with unmet need. Accordingly, it is a useful complement to the fixed time horizon used in our base case analysis. Steady-state results are only presented in the Appendix.

3.3 Decision problem

The relevant decision problem for our analysis is whether to invest in a CGT system-shift. This report does not seek to provide a complete characterisation or answering of this decision problem[1], but rather to support the generation of evidence to inform it. Nevertheless, it is important to consider the broader decision context in the design of our approach.

An important distinction can be drawn here between our approach and that of the National Institute for Health and Care Excellence (NICE). The decision problem faced by NICE relates only to the allocation of healthcare resources and is concerned primarily with the achievement of health outcomes. In contrast, our decision problem relates to public investment in general, beyond health and healthcare.

Approaches to addressing the decision problem described here are complementary to existing approaches to technology appraisal, and are not a replacement. In the scenarios that we consider, we assume that HTA processes remain in place. As such, the decision to invest in a particular technology is separate. Our analyses assumes that any future reimbursement of CGTs has been demonstrated to be cost-effective, and in focusing on health-related benefits, our analyses exclude the direct costs associated with CGT reimbursement.

Crucially, the decision problem does not relate to any specific technology or disease area, nor to the healthcare budget exclusively. Instead, it relates to investment in CGTs in general. However, evidence for the value of investment in CGTs is only available in relation to individual technologies, and we must rely on this evidence to inform our broader decision problem.

Our starting point in addressing the decision problem is to estimate the health-related value associated with a potential system-shift, with a focus in this report on the application of our methods to selected indications. We present our analyses of these indications as a series of case studies. Our objective in the case studies is to consider a broad range of technologies that address different disease areas and outcomes. We make realistic assumptions about CGTs that may come to market in the future and represent a plausible vision of an imminent CGT landscape.

[1] *Only health-related benefits for a small number of case studies are considered here. Non-health related benefits and costs will be considered in subsequent research.*

3.4 Scenarios: conservative vs optimistic

There is a great deal of uncertainty in the nature and scope of a potential CGT system-shift. In particular, we cannot be confident about the types and numbers of indications that may be treated with CGTs in the near future. Some CGTs are already approved for use, including for acute lymphoblastic leukaemia (ALL), beta thalassaemia (BT), and sickle cell disease (NICE, 2019, 2025, 2024b). In the context of these conditions, there is a well-developed evidence base characterising the potential health improvements. Nevertheless, the extent to which indications will expand, and the effectiveness of future CGTs in these indications, remains uncertain.

For other conditions, CGTs are in an early stage of development, and there is a lack of evidence to support the estimation of their effectiveness or the specific indications in which they are likely to be used.

In light of these elements of uncertainty, we consider two distinct scenarios in our analyses.

Scenario A considers the most credible scenario for the near-term, with conservative estimates of treatment effectiveness and therapeutic indication. Parameters and model assumptions are primarily derived from empirical estimates from clinical trials or in line with current use in similar disease areas. Where CGTs are currently available, estimates align with their current use and observed effectiveness.

Scenario B presents a more optimistic scenario, which may be most likely only in the long-term. This scenario will consider broader populations for eligibility, optimistic assessments of treatment-related outcomes, or optimistic expectations about the likelihood of pipeline products coming to market. For instance, this scenario may assume opportunities for early intervention, more sustained treatment effectiveness, or uncertain mechanisms of action. Nevertheless, estimates are informed by the best available evidence and scientific opinion.

3.5 Populations

Our analyses focus on populations that are anticipated to benefit from wider access to CGTs or may already be benefitting from access to CGTs. In specifying a realistic population, our analyses avoid simply including an entire patient population. It is unreasonable to assume that all potential patients within a broadly defined indication would be eligible and would benefit from CGTs.

In line with the scenarios described above, we adopt both less and more optimistic assumptions about patient eligibility. Scenario A aligns with samples specified in clinical trial information, economic evaluations, or technology appraisals. If this information is unavailable or insufficient, assumptions are specified to define a realistic population. Scenario B allows for a larger eligible population, or intervention at an earlier stage of the patient pathway.

Benefits to the UK economy, realised over a fixed time horizon, do not occur in a fixed population. The return on investment in a CGT system-shift would be achieved dynamically, as newly incident patient become eligible for treatment. Therefore, our analyses consider both the current prevalent patient population (at the point of investment) and future incidence. In some circumstances, the nature of a disease may dictate an exclusive focus on either incidence or prevalence alone. For example, if first-line treatments for newly incident cases are being considered, the prevalence of this disease

may not be relevant. In all cases, clear justification of the size and characteristics of both the prevalent and incident populations is provided.

In essence, populations and their characteristics are defined as those representing future patients within a given indication, that we anticipate would receive CGTs following the achievement of a CGT system-shift.

3.6 Interventions

The analysis compares treatment regimens before and after a CGT system-shift. Thus, the intervention being considered is access to CGTs for the patient population that has been defined. The comparator is a lack of access to CGTs, represented by current standard of care (SoC).

SoC is defined on the basis of targeted literature reviews for the population with the relevant indication for which we are estimating the value of CGTs. Literature searches were performed in PubMed and on the NICE website to identify relevant health technology appraisals or clinical guidelines. The review enabled us to define current care pathways, informing our methodology and the inputs to our analyses.

The health-related benefits of CGTs may be realised through a single hypothetical cell or gene therapy or a basket of available CGTs for the relevant indication. In our analyses, the nature of the CGTs available is informed by current medicines development pipelines, results of recent clinical trials, and HTA reports. This information is also supplemented by the results of targeted literature reviews, where studies may consider the adoption of CGTs in different settings, scenarios for access and effectiveness, or evidence relating to CGTs adopted for similar indications.

While specific technologies are referenced to inform the case studies, this analysis does not constitute an appraisal of individual interventions. Rather, these technologies are used to illustrate the types of benefits that may be achieved through a broader system shift, one in which CGTs are routinely accessible for appropriate indications. For each case study, we clearly outline the assumed clinical benefits of the CGTs considered, particularly whether they slow or halt disease progression, whether the CGT is considered curative and for whom, and any waning of effectiveness over time. Given the transformative potential of CGTs to replace ongoing management with one-time, potentially curative treatments, these case studies support an understanding of the value such a system shift could deliver.

3.7 Outcomes

All outcomes of value to society, that may be realised as a consequence of health improvements (including the value of those health improvements), are within the scope of our analysis. Our scope therefore extends beyond that of standard approaches to the evaluation of health technologies, which tend only to consider health outcomes and healthcare expenditures. Our analysis considers costs and benefits being realised outside of the health (care) sector, and accounts for the potential link between health and wider economic outcomes.

Outcomes that are within scope for our analysis include those that have previously been considered in economic evaluations that adopt a societal perspective, including patient and caregiver productivity effects, informal care time losses, and non-health sector costs (e.g. education) (Sittimart et al., 2024). The outcomes assessed are determined by

available evidence, with different outcomes depending on the nature of the disease and the characteristics of the population in which health gains are realised. Not all potentially relevant outcomes apply to all indications. For example, in indications affecting older populations, productivity benefits may be limited, whilst the carer burden may be significant. For working-age populations, the opposite may be true.

Changes in health outcomes can also have fiscal implications, for example, through the impact on government tax revenue and transfer payments such as pensions and welfare (OBR, 2024). While impacts on public finances are important to consider from a budget sustainability standpoint, our analysis focuses on the social value associated with a CGT system-shift and does not analyse the fiscal effects. Transfer payments are typically excluded from evaluations following Green Book methods.

We report the absolute values associated with CGT and SoC scenarios, as well as the incremental value associated with the CGT scenario. The value of outcomes may be positive or negative, but our focus in these analyses is on the incremental monetised value of the health-related outcomes associated with a CGT system-shift.

Outcomes that are within scope, and for which data are available, can be summarised in terms of to whom the value accrues: individuals (e.g. patients and their carers), systems (e.g. health and social care), and the national economy. Accordingly, outcomes may be realised at the micro (individual), meso (systems), or macro (economy) level.

Table 2 provides a non-exhaustive list of candidate outcomes that may be considered within each of these categories, and according to whether they are realised through health improvements and therefore, within scope for our current analysis.

Table 2 Examples of candidate outcomes

	INDIVIDUALS (Micro)	**SYSTEMS (Meso)**	**NATIONAL ECONOMY (Macro)**
HEALTH-RELATED (within scope of current study)	• Patient health-related quality of life • Patient longevity • Carer burden • Out-of-pocket costs	• NHS service use • Healthcare capacity gains • Unrelated future medical costs • Social care service use • Long-term care • Education	• Productivity • Public health indicators • Socioeconomic inequalities • National income
NON-HEALTH RELATED (future research)	• Treatment choice • Clinical trial participation	• Clinical expertise • Evidence generation • Research infrastructure	• Industrial expansion • Manufacturing capacity • Attracting investment • Export revenue • Job creation

The categorisation into individuals, systems, and national economy supports interpretation of the findings and the avoidance of double counting where outcomes may be observed at more than one level. As described in more detail in Appendix A, outcomes are valued monetarily and require careful interpretation: simply summing across categories and attributing this value as a macroeconomic benefit would result in double-counting. The categorisation also supports the assessment of value from different perspectives, and allows us to understand the different drivers of value.

Individuals

The individual (micro) level captures patient and caregiver gains, such as health-related quality of life improvements and life extension, which can be measures in terms of quality-adjusted life years (QALYs). In our analyses, we monetise QALYs associated with CGTs and SoC according to monetary valuations from the Green Book. Personal financial impacts, such as out-of-pocket costs for treatment, also accrue to individuals.

Systems

The system (meso) level includes net NHS and social care costs, including the avoidance of downstream expenditure and service use. For some indications, we identify evidence for productivity costs realised at the system level, for example when formal care funded by social care services could be displaced by informal caregiving by patients. Within the 'systems' category of outcomes, we also consider future unrelated medical costs. These are costs that are incurred for either conditions or treatments that are not related to the initial intervention and instead arise during the gains in life-years due to the intervention. This is particularly important since we are evaluating CGTs, which often treat a disease's underlying cause and can significantly extend survival. The inclusion of these costs is important to ensure life-extending interventions are not disproportionately favoured over those which primarily improve quality of life (Perry-Duxbury et al., 2020). As described above, direct costs associated with specific CGT therapies are excluded.

National economy

The national economy (macro) level values additional labour market participation, productivity impacts, and informal care contributions as monetary economic benefits. We monetise productivity impacts for CGT and SoC by measuring patient absenteeism, i.e. days of work lost during illness. Productivity impacts associated with family members' and informal caregivers' time use is estimated equivalently. Impacted time for patients and carers is valued based on the average income in the UK, as described in more detail in Appendix A.

4 Case studies

4.1 Case study selection

The process of selecting disease indications for the case studies was informed by an analysis of the likelihood of CGTs emerging, the feasibility of modelling the indications, the extent of disease burden, and a qualitative assessment of the potential research value. We sought to select a range of indications in terms of their characteristics and the populations affected.

Likelihood of CGTs emerging

We conducted a review and analysis of published pipeline data from BioMed Tracker (2024), filtering for disease groups, disease subgroups and indications with the highest number of CGT pipeline products. Maturity of the pipeline (e.g. trial phases) and treatment descriptions were also considered, alongside experts' opinions about the potential for CGT products in the pipeline to reach market for shortlisted indications.

Feasibility of modelling

Based on a PubMed search for published economic evaluations (as a proxy for feasibility of modelling), we removed indications with fewer than 10 PubMed results.

Disease burden

We assessed the population disease burden, comparing prevalence or incidence across all indications. We took into consideration disease severity, primarily based on DALY burden per 100,000 population. This information was balanced with an intention to also include rare diseases, which will have a lower DALY burden at the population level.

Potential research value

We then conducted a qualitative assessment of the potential research value of the proposed shortlist of indications in a collaborative workshop convening experts across multiple disciplines. An attempt was made to include a mix of indications for which therapeutic benefit is driven by life extension and indications for which quality of life improvement is likely to be the primary benefit. Further effort was made to include indications affecting a range of population age groups to showcase the variety of benefits which may accrue.

A range of indications

Following deliberative discussions, we included a range of indications in terms of characteristics and the populations affected. This included indications within the oncology disease area, given the high number of promising pipeline products in the disease group overall, as well as rare diseases, for which results on macroeconomic benefit may be transferable across other rare disease indications. We also included an 'aspirational' indication with a significant population disease burden (and a promising CGT pipeline). As an exploratory piece of work, our case study selection balances indications for which the exploration of a CGT system-shift may be especially relevant, either due to the viability of the current CGT pipeline or due to the potential scale of impact in disease areas with high unmet need.

The final case studies chosen for analysis were acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), beta-thalassaemia (BT), and Alzheimer's Disease (AD). Short summaries of the case studies are presented here (sections 4.2-4.5), with full details provided in the Appendix. Table 3 summarises the patient populations included in our study.

Table 3 Summary of eligible patient population

INDICATION	POPULATION	ELIGIBLE PATIENT SIZE (SCENARIO A)	ELIGIBLE PATIENT SIZE (SCENARIO B)
ALL	Paediatric and young adult patients (under 25 years) with relapsed or refractory (r/r) B-cell ALL.	Incidence and prevalence: 31 patients	
AML	Adult patients with untreated AML	Incidence and prevalence: 2,397 patients	Incidence and prevalence: 2,945 patients
BT	Patients aged 12 and older with transfusion-dependent beta thalassaemia	Prevalence: 352 patients Incidence: 8.18 patients	Prevalence: 920 patients Incidence: 21.4 patients
AD	Scenario A: Adults aged 65 and older with mild dementia due to AD (mild AD) Scenario B: Adults aged 65 and older with mild cognitive impairment due to AD (MCI-AD)	Incidence: 97,316 patients	

4.2 Acute lymphoblastic leukaemia (ALL) Disease overview

ALL is an aggressive haematological malignancy characterised by the clonal proliferation of immature lymphoid cells, known as lymphoblasts, in the bone marrow and peripheral blood. This uncontrolled proliferation impairs normal blood cell production, leading to a range of clinical symptoms (Terwilliger and Abdul-Hay, 2017).

ALL is most prevalent in children, although it can also affect adults, particularly those over 40 years of age. Leukaemia is the most prevalent childhood cancer in the UK and ALL is the predominant form of childhood leukaemia, accounting for about 78% of all leukaemia diagnoses in children in the UK (Children with Cancer UK, 2025). Globally, over 150,000 new cases of ALL and over 40,000 deaths were reported in 2019, with the highest incidence in children aged 1—4 years (Pagliaro et al., 2024a; Zhang et al., 2023).

Standard of care for ALL follows a multi-phase pathway beginning with induction chemotherapy to achieve remission, followed by consolidation and maintenance phases over up to three years, alongside CNS prophylaxis. In cases of relapse or refractory disease, patients can be treated with CAR T-cell therapy which targets CD19-positive leukaemia cells. Further detail on treatment pathways for the patient population is provided in Appendix B.

Health-related quality of life (HRQoL) studies in ALL highlight consistent impairment during treatment and variable recovery post-therapy. ALL and its treatment can lead to fatigue, pain, and mobility issues, which can negatively affect mental health and school functioning (Iyer et al., 2015; Shalitin et al., 2018; Chow et al., 2010). This burden extends to caregivers: up to 94% report work disruption, with one study estimating 17.3 missed workdays in the first month post-diagnosis (Bona et al., 2014; Fluchel et al., 2014).

PICO and scenarios

Scenarios:

- **Scenario A:** parameters and assumptions are derived from clinical trials, published HTA appraisals and economic models published in the literature.
- **Scenario B:** explores plausible optimistic estimates and assumptions largely based on benefits to the economy that arise from health improvements associated with CGT, such as improved socioeconomic outcomes and reduced caregiver burden.

Population: Paediatric and young adult patients (under the age of 25 years) with relapsed (either after a transplant or after two or more lines of treatment) or refractory (r/r) B-cell ALL. The mean age is 12 years, with 43.04% of the population female.

Intervention: We model the CGT as CAR-T therapy, using effectiveness data related to tisagenlecleucel. The intervention is delivered as a single, one-time dose of a CGT. We include the costs associated with pre-treatment procedures (leukapheresis to collect T cells), lymphodepleting chemotherapy to enhance CAR-T efficacy and bridging chemotherapy to stabilize disease while CAR-T cells are manufactured.

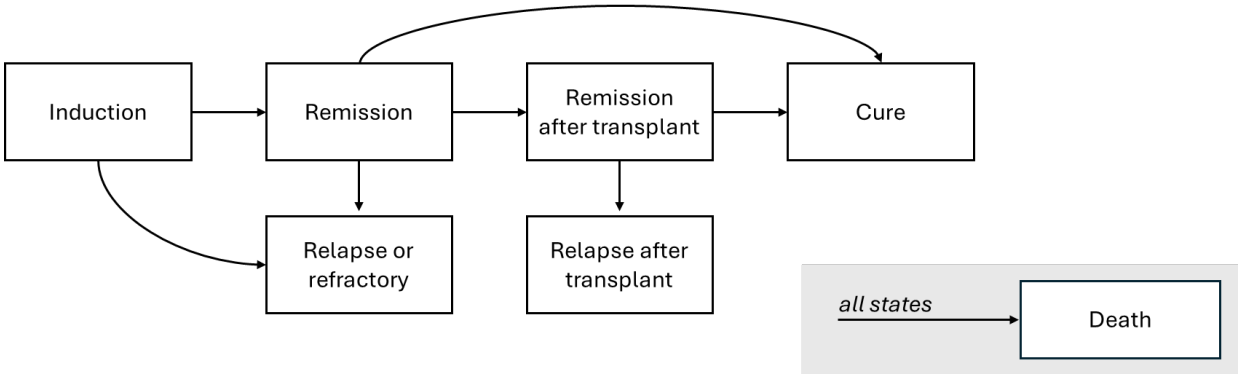
Comparator: A basket of blinatumomab (an immunotherapy) and salvage chemotherapy. Blinatumomab, a bispecific T-cell engager targeting CD19, is frequently used in paediatric patients with primary refractory disease or those in second or subsequent relapse. Salvage chemotherapy, typically consisting of intensive multi-agent regimens such as FLAG-IDA, continues to be widely used for patients who are ineligible for, or have previously failed, immunotherapy.

Outcomes: Life years gained, QALYs, total healthcare costs, productivity losses for the caregiver. Broader socioeconomic outcomes, such as educational outcomes, are not included due to lack of data; see Appendix B for further details.

Model structure

The model structure, as shown in Figure 2, follows a seven-state cohort transition model, similar to an existing cohort model published for paediatric and young adult patients with relapsed or refractory B-cell ALL (Lin et al., 2018).

Figure 2 ALL model structure based on Lin et al., 2018



Results

Table 4 shows that in conservative scenario A, health gains to individuals from CGT therapy (relative to SoC) total an additional 159 QALYs, delivering additional value to the sum of £11m over the 10-year period. The benefit to the national economy amounts to £600k over the same period.

Table 4 Scenario A results, ALL

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£98,077,925	£86,937,484	£11,140,441
	Systems	-£1,056,479	-£1,228,165	£171,686
	National economy	-£36,443,123	-£37,043,264	£600,141
HEALTH OUTCOMES	QALYs	1,401	1,242	159 QALYs
	Life years	1,659	1,539	120 LYs
	Deaths	22	65	43 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

Table 5 presents results from a more optimistic scenario B, where the benefit to society is estimated at £16m over the 10-year period. Health gains to individuals and system benefits remained unchanged, as no assumptions related to these impacts were altered.

Steady-state (annual) estimates for ALL for scenario A indicate that gains to individuals from CGTs (relative to SoC) have a value of £335 million per year. Further results are presented in Appendix B.

Table 5 Scenario B results, ALL

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£98,077,925	£86,937,484	£11,140,441
	Systems	-£1,056,479	-£1,228,165	£171,686
	National economy	-£36,443,123	-£52,747,641	£16,304,518
HEALTH OUTCOMES	QALYs	1,401	1,242	159 QALYs
	Life years	1,659	1,539	120 LYs
	Deaths	22	65	43 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

4.3 Acute myeloid leukaemia (AML)

Disease overview

AML is a rapidly progressing haematological malignancy characterised by the abnormal proliferation of immature myeloid cells (Juliusson, Lehmann and Lazarevic, 2021). It is the most prevalent form of acute leukaemia in adults, with a higher incidence observed in individuals over 60 years of age (Vakiti, Reynolds and Mewawalla, 2024). In the UK, AML accounts for around 2,945 new cases each year (Cancer Research UK, 2019). Five-year survival rates in the UK vary by age: over 35% for patients under 60 years and below 15% for those over 60 (Haematological Malignancy Research Network (HMRN), 2024).

Standard of care for AML involves intensive chemotherapy, and in selected cases, chemotherapy combined with HSCT (Kantarjian et al., 2021). The disease and its treatments can substantially affect patients' health-related quality of life (HRQoL) (Korol et al., 2017). Physical symptoms commonly include fatigue, pain, and dyspnoea. Psychological distress, such as anxiety and depression, is often reported amongst patients treated with 'intensive' chemotherapy requiring prolonged hospitalisations (El-Jawahri et al., 2019; Lockwood et al., 2020). A study on work absenteeism and disability among AML patients and their caregivers reported significant impacts on workplace absence and disability days (Pandya et al., 2024).

PICO and scenarios

Scenarios:

- **Scenario A:** parameters and assumptions are derived from clinical trials or in line with current use in similar indications, such as ALL. The population receiving CAR-T therapy is based on the CAR-T population identified in the NICE appraisal of tisagenlecleucel. The probability of resistant disease amongst patients is informed by empirical estimates associated with current antibody-based therapy for AML (Russell-Smith et al., 2021). A proportion of CAR-T patients are assumed to receive HSCT after relapse in line with estimates for current antibody-based therapy for AML (Russell-Smith et al., 2021).

- **Scenario B:** All untreated AML patients within the assessed population will be eligible for CAR-T treatment. Lower probabilities of resistant disease are assumed amongst CAR-T patients, based on evidence in the literature that CAR-T therapies are associated with higher rates of complete remission compared to SoC (Cappell and Kochenderfer, 2023a). It is assumed that CAR-T patients do not undergo HSCT treatment.

Population: Adult patients with untreated AML. We model the mean age to be 61.2 years, with 50.93% of the population female. This is in line with similar NICE appraisals of therapies for untreated AML (Russell-Smith et al., 2021). We focus exclusively on an incident population of AML.

Intervention: We model the CGT as CAR-T therapy, given that CAR-T therapies are currently in development for AML and are successfully used to treat related cancers. The intervention involves a one-off single dose of a CGT, along with the costs of pre-treatment (leukapheresis to obtain T-cells, conditioning chemotherapy to enhance CAR-T efficacy and bridging chemotherapy to stabilise disease) and administration.

Comparator:

- For 70% of patients: Induction: 7+3 regimen with cytarabine and daunorubicin; Consolidation: High dose cytarabine; Subsequent therapies: FLAG-IDA chemotherapy regimen or non-curative therapies.

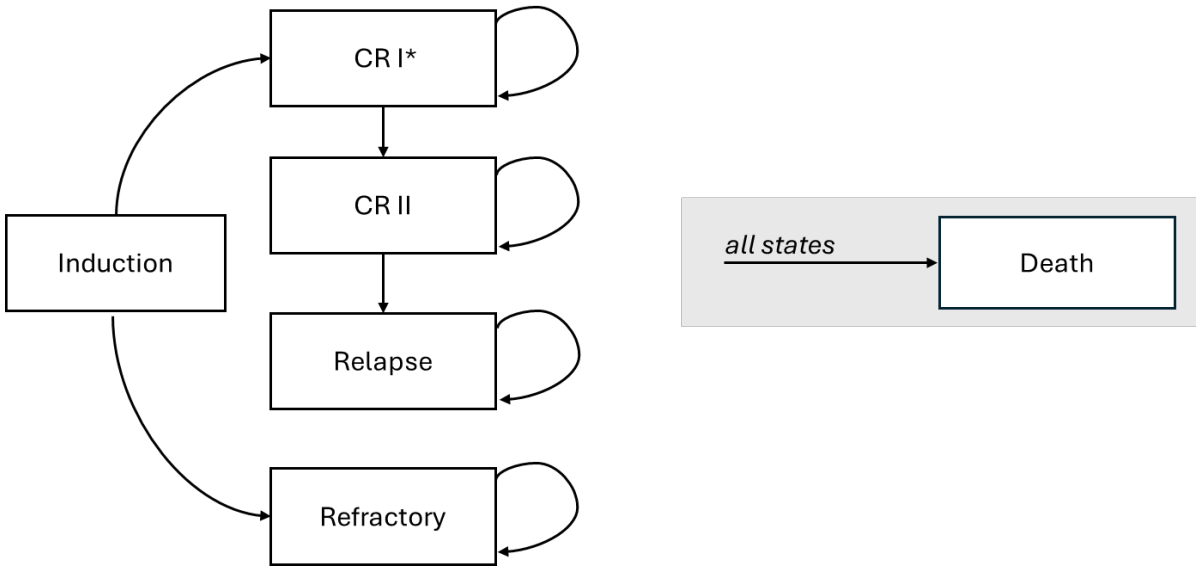
- For 30% of patients with FLT3 mutations: Induction: 7+3 regimen with cytarabine and daunorubicin, with quizartinib; Consolidation: High dose cytarabine, with quizartinib; Maintenance: Quizartinib only; Second-line treatment: FLAG-IDA chemotherapy regimen or non-curative therapies.

Outcomes: Life years gained, QALYs, total healthcare costs, productivity losses for the patient and caregiver.

Model structure

The model structure, as shown in Figure 3 follows a five-state cohort transition model, similar to existing cohort models published for AML therapies (Russell-Smith et al., 2021).

Figure 3 AML model structure, based on Russell-Smith et al., 2021



Results

Table 6 shows that in conservative scenario A, health gains to individuals from CGT therapy (relative to SoC) total an additional 8,335 QALYs, with additional value of £583m over the 10-year period. Gains to the health system are of a similar magnitude, around £464m. The value to the national economy amounts to £5.5m.

Table 7 shows that in the more optimistic scenario B, the individual gains from CGT therapy provide an additional 10,367 QALYs and a value of £726m. Systems benefits equate to £616m, and national economy value is £8.4m.

Steady-state (annual) estimates for AML for scenario A indicate that health gains to individuals from CGT therapy (relative to SoC) equal a gain of £255 million, a systems-

level value of £410 million and a national economy value of £4.3 million per year. Further results are presented in Appendix C.

Table 6 Scenario A results, AML

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£7,049,307,907	£6,465,890,707	£583,417,200
	Systems	-£866,020,112	-£1,329,615,158	£463,595,047
	National economy	-£3,834,831,012	-£3,840,358,757	£5,527,745
HEALTH OUTCOMES	QALYs	100,704	92,370	8,335 QALYs
	Life years	130,791	130,713	78 LYs
	Deaths	882	922	40 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

Table 7 Scenario B results, AML

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£8,669,016,327	£7,943,354,677	£725,661,651
	Systems	-£1,017,319,160	-£1,633,433,856	£616,114,695
	National economy	-£4,709,441,732	-£4,717,885,451	£8,443,719
HEALTH OUTCOMES	QALYs	123,843	113,476	10,367 QALYs
	Life years	160,700	160,581	120 LYs
	Deaths	1,071	1,132	61 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

4.4 Beta thalassaemia
Disease overview

Beta thalassaemia (BT) is an inherited disorder caused by mutations that reduce or eliminate beta-globin production, impairing haemoglobin synthesis and leading to anaemia (NICE, 2024a). Severity ranges from non-transfusion-dependent (NTDT) to transfusion-dependent beta thalassaemia (TDT), the latter requiring lifelong red blood cell transfusions and iron chelation therapy (Thalassaemia Internation Federation, 2021). TDT is associated with serious complications, reduced life expectancy, and substantial healthcare costs (NICE, 2024a). Life expectancy for individuals with TDT remains significantly lower than the general population, with estimates indicating that 40% of patients in the UK die before reaching the age of 50 (Weidlich, Kefalas and Guest, 2016).

TDT also significantly impacts quality of life and productivity. Many patients report pain, anxiety, and difficulty with daily activities (Li et al., 2022a), though standard tools like EQ-5D-5L may underestimate disease burden (Boateng-Kuffour et al., 2024). The condition affects employment, with only 65.4% of patients working compared to 75.5% in the

general UK population (ONS, 2024a), and high rates of absenteeism (19.5%) and presenteeism (34.4%) (Li et al., 2022a).

PICO and scenarios

Scenarios:

- **Scenario A:** is identical to the population in the NICE appraisal of exa-cel, specifically patients over the age of 12 who have TDT who are fit for transplant and without a human leukocyte antigen (HLA)-matched sibling donor (NICE, 2024a). The proportion of patient's achieving transfusion independence (TI) is in-line with the NICE evaluation of exagamglogene autotemcel (exa-cel), 92.6%.

- **Scenario B:** considers the entire TDT population being eligible for treatment, thereby assuming a larger pool of patients able to benefit from the CGT. In addition, 100% of patients achieve TI.

Population: Adult patients with TDT. We model the mean age to be 25 years, with 52.1% of the population female. This age threshold and disease definition broadly align with the population used in the NICE appraisal of exa-cel (NICE, 2024a) and the Institute for Clinical and Economic Review (ICER) appraisal of betibeglogene autotemcel (beti-cel) (Beaudoin et al., 2022).

Intervention: The intervention evaluated in this analysis is a hypothetical one-time cell or gene therapy (CGT) that aims to address the underlying cause of BT, leading to a transfusion-independent, disease-free state. While not representing a specific marketed therapy, its assumed effectiveness and characteristics are informed by clinical data for exa-cel and beti-cel (NICE, 2024a; Beaudoin et al., 2022).

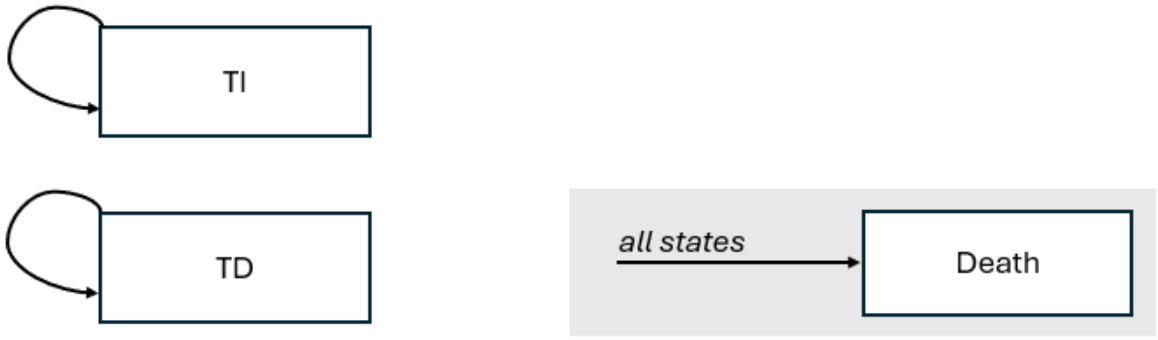
Comparator: A regular programme of red blood cell (RBC) transfusions, alongside iron chelation therapy (ICT) and the monitoring and management of complications (NICE, 2024a).

Outcomes: Life years, QALYs, total healthcare costs, productivity losses for the patient and caregiver.

Model structure

The model structure, as shown in Figure 4 follows a cohort three-state transition model, similar to existing cohort models published for BT CGTs (NICE, 2024a; Beaudoin et al., 2022). The three states include transfusion independent (TI), transfusion dependent (TD), and death.

Figure 4 Beta thalassaemia model diagram adapted from (Beaudoin et al., 2022; NICE, 2024a)



Results

Table 8 shows that in conservative scenario A, health gains to individuals from CGT therapy (relative to SoC) total an additional 747 QALYs, delivering additional value to the sum of £52m over the 10-year period. System-level gains are of a similar magnitude, around £74m. The benefit to the national economy amounts to £51m over the same period.

Table 9 shows that in the more optimistic scenario B, the health gains from CGT therapy provide an additional 2118 QALYs, with the value of these health benefits being £148m, benefits to the health system £211m, and society £144m.

Steady-state (annual) estimates for BT for scenario A indicate that health gains to individuals from CGT therapy (relative to SoC) equal a gain of 163 QALYs, with an individual-level value of £11m, a systems-level value of £5.7m, and a national economy value of £3.4m per year. Further results are provided in Appendix D.

Table 8 Scenario A results, BT

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£247,588,220	£195,311,700	£52,276,520
	Systems	- £15,636,841	- £89,759,186	£74,122,345
	National economy	- £4,902,476	- £55,448,235	£50,545,759
HEALTH OUTCOMES	QALYs	3537	2790	747 QALYs
	Life years	4298	4269	29 LYs
	Deaths	3.40	10.9	7.5 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

Table 9 Scenario B results, BT

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£658,919,573	£510,618,825	£148,300,748
	Systems	-£24,072,975	-£234,664,539	£210,591,564
	National economy	-£1,325,995	-£144,962,707	£143,636,712
HEALTH OUTCOMES	QALYs	9413	7295	2118 QALYs
	Life years	11243	11162	111 LYs
	Deaths	7.19	28.4	21.21 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

4.5 Alzheimer's disease

Disease overview

Alzheimer's disease (AD) is an irreversible and neurodegenerative brain condition characterised by significant and progressive cognitive decline (Davis et al., 2018). Alzheimer's is the most common form of dementia (Davis et al., 2018). Dementia incidence is on the rise, and recent estimates project that by 2040, there will be 1.7 million dementia cases in England and Wales (Chen et al., 2023).

Standard treatment for AD includes AChE inhibitors for mild to moderate stages and Memantine for severe cases or when AChE inhibitors are not suitable (NHS, 2018). Recent advances have led to the development of disease-modifying therapies that target the underlying biology of the disease, including gene therapies.

Alzheimer's disease has significant implications for patient and caregiver quality of life. The progressive reduction in patients' independence and quality of life subjects caregivers to increased emotional distress, poor mental and physical well-being, decreased workplace productivity, and loss of earnings and savings (Herring et al., 2021; Robinson et al., 2020). The economic burden of dementia (and AD) has been found to more substantially impact the social care sector than the healthcare sector, and increases with the severity of dementia (Wittenberg et al., 2019). For example, healthcare costs are estimated to only make up 14% of total AD costs, whereas 77% of total AD costs are spent on social care and unpaid care (Carnall Farrar, 2024).

PICO and scenarios

Scenarios:

The primary differences between scenarios A and B for Alzheimer's Disease are the stage at which individuals enter the model and the point at which the CGT intervention is delivered.

- **Scenario A:** individuals enter the model and receive the CGT at the mild AD stage.

- **Scenario B:** individuals enter the model and the CGT is delivered at the mild cognitive impairment due to AD (MCI-AD) stage (Herring et al., 2021). MCI due to AD is a pre-dementia phase of AD, defined by noticeable memory problems or impaired judgment or decision-making, which does not affect independence of function in daily life nor meet the criteria for dementia (Davis et al., 2018). Modelling an intervention targeting MCI due to AD would be more effective at preventing disease progression and subsequent costs (Kieu and Look, 2023). However, estimates of the MCI-AD population may be less accurate due to lack of diagnosis at that early stage (Davis et al., 2018; NICE, 2023). We assume that the same incident population in scenario A is diagnosed and treated earlier in scenario B.

Population: Adults aged 65 and older with mild dementia due to AD (mild AD) in scenario A or mild cognitive impairment due to AD (MCI-AD) in scenario B. An estimated 982,000 people are living with dementia in the UK, with 49.7% (488,054) estimated to have mild dementia. We estimated an incident population of 97,316 per year, using the average number of new cases of Alzheimer's per year in England during pre-COVID years and multiplying it by a scaling factor to estimate the UK total (NICE, 2023, p.202). We assume that newly incident cases are categorised as mild AD (or MCI-AD in the case of scenario B).

Intervention: The intervention is access to one or more hypothetical gene therapies that deliver a copy of the apolipoprotein E (APOE)-e2 gene into the central nervous system (Lexeo Therapeutics, 2023; Serrano-Pozo, Das and Hyman, 2021), in addition to SoC for management of AD symptoms. Patients receive the gene therapy once on entry to the model (Kieu and Look, 2023).

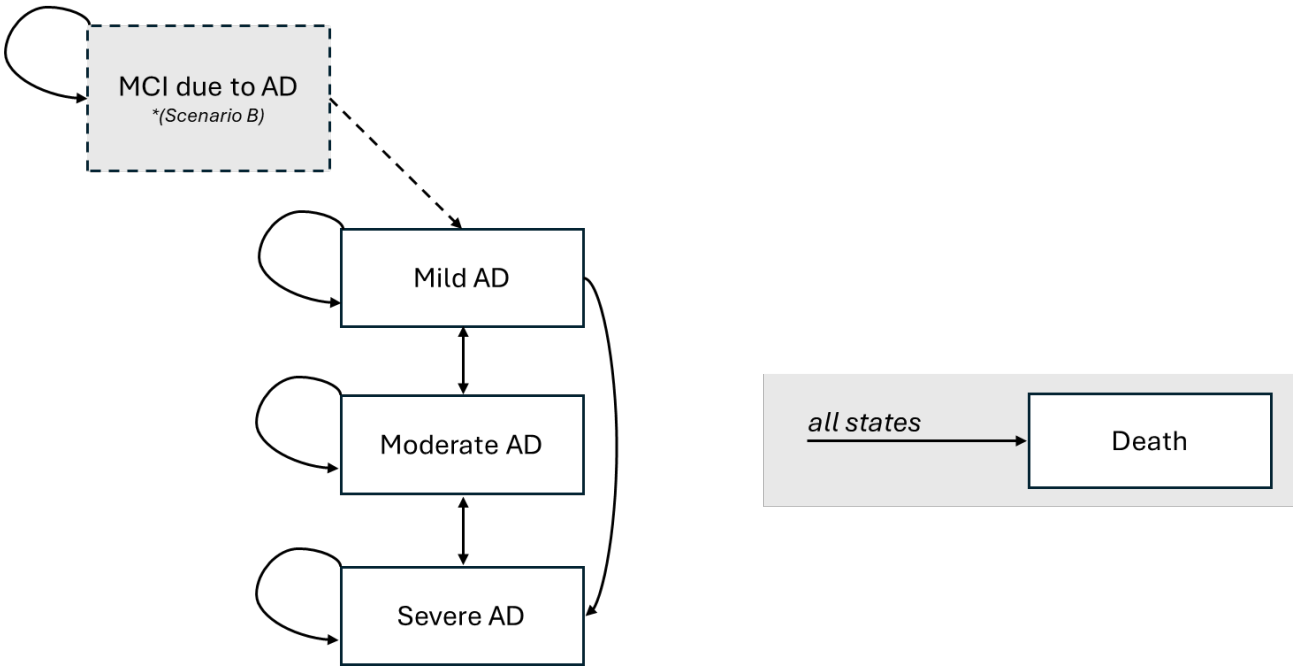
Comparator: Varies based on the severity of the disease, but consists of medication to manage symptoms but not to alter disease progression. For managing mild to moderate AD, the SoC involves acetylcholinesterase (AChE) inhibitor monotherapies (e.g. donepezil, galantamine and rivastigmine). Patients with severe AD or with moderate AD who are intolerant of or have a contraindication to AChE inhibitors are recommended memantine monotherapy.

Outcomes: Life years gained, QALYs, total healthcare costs, productivity losses for the patient and caregiver.

Model structure

The model structure is shown in Figure 5. A similar model structure has been used previously in the economic evaluation of disease-modifying therapies for AD, as well as for non- disease-modifying therapies s for AD (Davis et al., 2018; Kieu and Look, 2023; Green et al., 2019; Boustani et al., 2022).

Figure 5 Alzheimer's Disease model diagram based on Transition probabilities from (Potashman et al., 2021)



Note: diagram includes MCI-AD state due to its inclusion in scenario B

Results

Table 10 shows that in conservative scenario A, health gains to individuals from CGT therapy (relative to SoC) total an additional 412,821 QALYs, delivering additional value to individuals of £40bn over the 10-year period. Gains to health and social care systems are around £19bn. The benefit to the national economy amounts to £21bn over the same period.

Table 11 shows that in the more optimistic scenario B, the health gains from CGT therapy provide an additional 454,637 QALYs, with a value of these health (micro) benefits at £45bn, benefits to health and social care systems £27bn, and to the national economy £27bn.

Steady-state (annual) estimates for AD for scenario A indicate that health gains to individuals from CGT therapy (relative to SoC) equal a gain of 68,049 QALYs, with an individual-level value of £5.3bn, a systems-level value of £792 million, and a national economy value of £956 million per year. Further results are provided in Appendix E.

Table 10 Scenario A results, Alzheimer's disease

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£214,220,869,619	£174,666,993,879	£39,553,875,739
	Systems	-£268,066,331,663	-£287,279,607,754	£19,213,276,091
	National economy	-£217,857,016,757	-£239,329,418,718	£21,472,401,962
HEALTH OUTCOMES	QALYs	4,640,989	4,228,168	412,821 QALYs
	Life years	8,913,805	8,703,217	210,588 LYs
	Deaths	555,850	618,368	62,518 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

Table 11 Scenario B results, Alzheimer's disease

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£390,858,015,062	£345,821,035,374	£45,036,979,688
	Systems	-£163,894,215,575	-£190,802,391,865	£26,908,176,291
	National economy	-£121,844,807,713	-£148,841,729,356	£26,996,921,644
HEALTH OUTCOMES	QALYs	6,494,299	6,039,662	454,637 QALYs
	Life years	10,100,404	9,863,536	236,868 LYs
	Deaths	238,643	337,532	98,888 deaths averted

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.
Positive figures represent gains during the time horizon, while negative figures represent losses.

5 Implications and next steps

5.1 Summary of findings

Under the conservative scenario A, widening access to CGTs is projected to create value between £20 billion and £40 billion across the four indications, depending on the category of value considered. Due to the risk of double-counting across categories, it is important to consider the individual, system, and national economy results separately, as shown in Table 12.

Alzheimer's disease dominates the aggregated results, contributing £39.6 billion in individual benefits, £19.9 billion in health-system savings, and £21.5 billion in wider-economy gains. The costs of dementia in the UK have been estimated at around £42 billion per year (Carnall Farrar, 2024): the 10-year gains estimated in our base case analysis represent a significant proportion of the estimated burden of disease.

At the other extreme, acute lymphoblastic leukaemia (ALL) generates value through a very small patient cohort, illustrating that rarity need not be a barrier to positive social returns. Beta-thalassaemia (BT) stands out as the only case in which system savings (£74 million) exceed individual gains (£52 million), confirming transfusion independence as a major budgetary lever. Acute myeloid leukaemia (AML) delivers a more balanced mix of individual value (£583 million) and system offsets (£463 million).

If services can move closer to the more optimistic scenario B, the ten-year benefit envelope widens by almost 50% in some cases. The largest incremental uplift again comes from Alzheimer's disease, where faster uptake and improved durability of effect may raise total gains by as much as 38%. Every other indication also posts material gains in the more optimistic scenario. AML adds a further £146 million across individual and system value. In practical terms, these figures imply that each year of delay in rolling out CGTs may cost society several billion pounds.

Table 12 Main findings

	INDIVIDUALS		SYSTEMS		NATIONAL ECONOMY	
Scenario:	A	B	A	B	A	B
ALL	£11 m	£11 m	£0.1 m	£0.1 m	£0.6 m	£16 m
AML	£583 m	£725 m	£463 m	£616 m	£5.5 m	£8.4 m
BT	£52 m	£148 m	£74 m	£211 m	£51 m	£144 m
AD	£39.6 bn	£45.0 bn	£19.9 bn	£27.6 bn	£21.5 bn	£27.0 bn

Estimates represent the incremental monetised value of outcomes over 10 years

These analyses incorporate immediately relevant and achievable expansion of access to CGTs (e.g. for AML) with more ambitious and longer-term expectations about the availability of CGTs (e.g. for AD). The disease areas that we have explored also differ significantly in terms of the nature of existing healthcare and the characteristics of patients. This heterogeneity in the selection of indications supports a nuanced and realistic assessment of the drivers of value for a CGT system-shift. Notably, the drivers of

value differ significantly across indications. For BT, there is substantial potential for health system savings through reduced red blood cell transfusions, iron chelation therapy, and complications as patients achieve transfusion independence. In contrast, the AML and AD case studies show value predominantly through health outcomes, with very large QALY gains in each scenario.

These findings demonstrate that CGTs can create substantial value at multiple levels, from direct patient health benefits to healthcare system savings and broader economic impacts. The heterogeneity of benefits across indications highlights the need for a holistic assessment approach when considering investments in CGTs.

While our findings demonstrate substantial value associated with a CGT system-shift, it is important to emphasise that these results should not be used to infer the value of any specific technology. In particular, for indications such as ALL and BT, where CGTs are already available, our estimates must not be misread as suggesting that the NHS is currently paying more than these therapies are worth. This would be a misinterpretation. Our analyses focus on small populations and adopt a conservative, short- to medium-term time horizon. Our base case analysis does not capture benefits beyond 10 years, including potential lifetime health gains, avoided long-term costs, or long-term broader societal impacts. Moreover, our approach is fundamentally different from health technology assessment: it is not designed to inform pricing or reimbursement decisions for individual products. Instead, it provides a system-level perspective on the potential value of coordinated investment in CGT infrastructure and access. As such, our results should be interpreted as indicative of the value of a system-shift, and not as a judgement on the cost-effectiveness of specific therapies.

For each of our case studies, we compare our results with published economic evaluations. For paediatric B-cell ALL, we modelled tisagenlecleucel (Kymriah) and compared results with a NICE technology appraisal and two US studies, finding our estimates of incremental QALYs and life years were more conservative, likely reflecting our shorter time horizon and cautious assumptions. In AML, where no CAR-T therapies are yet approved, we compared our proposed therapy with azacitidine evaluations, observing broadly comparable QALYs but greater benefit for CAR-T consistent with its curative potential, while our slightly lower life year estimates reflect conservative survival assumptions due to limited CAR-T data in this indication. For BT, our one-time gene therapy model informed by exa-cel data showed clinical outcomes that aligned well with three relevant economic evaluations, with our total QALYs falling between existing studies and reinforcing our disease model's robustness despite healthcare system differences limiting cost comparisons. For AD, our hypothetical gene therapy analysis showed incremental QALYs and life years of similar magnitude to a comparable US-based evaluation when using matched methodology and time horizons, providing validation for our modelling approach across this diverse therapeutic portfolio. Further detail is provided in Appendices B to E.

5.2 Research agenda

The research presented in this report constitutes the foundation for establishing the return on investment of a CGT system-shift. Our methodology provides a framework for evaluating the health-related benefits of CGTs that can be extended to other disease areas and adapted to other similar health technology-related system-shifts. Future research should extend this analysis in several important directions:

- A subsequent stage of this analysis will evaluate benefits beyond those associated with health gains, including research and innovation ecosystem benefits, such as increased employment in healthcare and life sciences sectors, attraction of commercial trials to the UK, and knowledge spillovers. Establishing the UK as a leader in CGT development could significantly boost the life sciences sector and in turn the

national economy. Clinical trials in 2022 alone generated an estimated £7.4 billion and supported around 65,000 jobs in the UK, with wider spillovers leading to higher NHS revenue, improved patient outcomes and the generation of academic publications (ABPI, 2024). CGTs involve advanced manufacturing techniques, creating highly skilled job opportunities in the UK economy.

- A comprehensive evaluation must also include the costs of achieving a CGT system-shift, including infrastructure development, workforce training, and capacity building. This will enable calculation of a full return on investment and benefit-cost ratio.

- Further work may also examine additional disease areas and indications where CGTs are in development, expanding the evidence base for the value of a system-shift. The 2024 BioMed Tracker identifies 36 indications with Phase 3 CGT trials, ranging from cancers and rare diseases to chronic and acute conditions with long-term impacts. Each of these indications likely imposes a distinctive combination of burdens on individuals, systems, and national economies. Our findings are specific to the four case studies selected and thus our assessment of the health-related benefits of a system-shift is incomplete. While we illustrate the different types and potential magnitudes of the health-related benefits of CGT, extending this analysis to include indications with a mature CGT pipeline would offer a broader illustration of the potential value of a system shift.

- Future analyses will need to address the challenge of aggregation across indications and across categories of value.

The generalisability of our approach means that it can be adapted to evaluate other healthcare innovations requiring system-level changes beyond individual technology assessments. Inevitably, an ambitious analysis of this kind is associated with some limitations. We do not seek to develop the most nuanced specification of clinical pathways and disease progression in our models, and do not account for individual variations in treatment needs or response. Future research should consider the limitations associated with this trade-off.

5.3 Policy implications

Our analysis employs a novel perspective to a challenging decision problem, seeking to inform national level investment decisions to support the achievement of a CGT system-shift. Our approach and methodology are grounded in best-practice guidance for both public investment decision-making and decision modelling techniques. Our societal perspective analysis provides a complementary approach to traditional HTA methods, which typically focus on health gains and healthcare expenditures. For transformative technologies like CGTs, this broader perspective can better inform national-level investment decisions. Government decision-makers should consider frameworks that capture the full range of benefits demonstrated in our case studies - from direct health improvements to healthcare resource savings and productivity gains.

The substantial benefits identified may justify significant public investment in CGT infrastructure and capacity building, with clear potential for returns across multiple sectors of the economy. The diverse value profiles across indications suggest that policy planning should anticipate emerging CGT therapies across a range of disease areas, rather than focusing exclusively on areas where CGTs are currently available.

For a CGT system-shift to occur, stakeholders need to have a better understanding of the CGT paradigm and the benefits of building the necessary organisational and societal culture. This may require significant investment, but such investment should not be limited to the healthcare sector. As CGT culture becomes embedded, knowledge spillovers

(externalities) may emerge surrounding how CGT products work and can be delivered within the healthcare system. Capacity will be needed to efficiently absorb these spillovers.

It will be important to explore practical approaches that can support bringing CGTs to market, which might require changes in policy. This may include novel payment approaches such as annuitisation, outcomes-based payments, and indication-based pricing models, which could support sustainable implementation of CGTs (Firth et al., 2021).

5.4 Conclusion

Wider access to cell and gene therapies could be supported by a shift in technology, infrastructure, behaviour, and policy, which in turn could realise diverse health-related benefits. Such a system shift is likely to require investment beyond the reimbursement of individual health technologies.

Our analyses demonstrate the potential health-related value of such investments, illustrated using four heterogeneous case studies. Health-related benefits associated with access to CGTs are realised at different levels, from the individual patient, to health and social systems, to the wider economy. The magnitude of these benefits differs across technologies, ranging from around £5.3 million over 10 years for macro-level benefits associated with CGT treatment of AML (conservative scenario A) to around £40 billion over 10 years for micro-level benefits associated with CGT treatment of Alzheimer's disease (also under conservative scenario A).

These estimates represent the total value that may be realised from the health-related benefits associated with CGTs in each indication. They provide initial estimates for value associated with health gains that can be realised for the economy per indication within the short to medium term. When combined with future research on wider economic benefits and investment requirements, these findings will provide a comprehensive assessment of the case for a CGT system-shift in the UK.

References

ABPI, 2024. *The value of industry clinical trials to the UK - extended report*. [online] Available at: https://www.abpi.org.uk/publications/the-value-of-industry-clinical-trials-to-the-uk-extended-report/. [Accessed 11 Dec. 2024].

Adkins, S., 2019. CAR T-Cell Therapy: Adverse Events and Management. *Journal of the Advanced Practitioner in Oncology*, 10(Suppl 3), pp.21—28. DOI: 10.6004/jadpro.2019.10.4.11.

Advanced Therapy Treatment Centres, 2022. *National cell and gene therapy vision for the UK: a recommended overview of the content of a national vision document*. [online] Available at: https://www.theattcnetwork.co.uk/wp-content/uploads/2022/03/National-Cell-and-Gene-Therapy-Vision-for-the-UK.pdf. [Accessed 7 Feb. 2025].

Alzheimer's Research UK, 2022. *The Impact of Dementia on Women*. [online] Alzheimer's Research UK. Available at: https://www.alzheimersresearchuk.org/about-us/our-influence/policy-work/reports/the-impact-of-dementia-on-women/. [Accessed 10 Jan. 2025].

Alzheimer's Research UK, 2023. *Towards Brain Health Equity*.

American Society of Gene + Cell Therapy, 2023. *Cell Therapy Basics* /. [online] ASGCT.org. Available at: https://patienteducation.asgct.org/gene-therapy-101/cell-therapy-basics. [Accessed 24 Feb. 2025].

Angelucci, E., Muretto, P., Nicolucci, A., Baronciani, D., Erer, B., Gaziev, J., Ripalti, M., Sodani, P., Tomassoni, S., Visani, G. and Lucarelli, G., 2002. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. *Blood*, 100(1), pp.17—21. DOI: 10.1182/blood.v100.1.17.

Angioli, R., Capriglione, S., Aloisi, A., Miranda, A., de Cicco Nardone, C., Terranova, C., Adrower, R. and Plotti, F., 2015. Economic Impact Among Family Caregivers of Patients With Advanced Ovarian Cancer. *International Journal of Gynecological Cancer*, 25(8), pp.1541—1546. DOI: 10.1097/IGC.0000000000000512.

Asaria, M., 2017. *Health care costs in the English NHS: reference tables for average annual NHS spend by age, sex and deprivation group*. Research Papers. [online] Centre for Health Economics. Available at: https://ideas.repec.org//p/chy/respap/147cherp.html. [Accessed 6 May 2025].

Asay, G.R.B., 2016. Absenteeism and Employer Costs Associated With Chronic Diseases and Health Risk Factors in the US Workforce. *Preventing Chronic Disease*, [online] 13. DOI: 10.5888/pcd13.150503.

Beaudoin, F., Richardson, M., Synnott, P., Lancaster, V., Fluetsch, N. and Herce-Hagiwara, B., 2022. *Beta Thalassemia*. [online] ICER. Available at: https://icer.org/beta-thalassemia-2022/. [Accessed 2 Oct. 2024].

Besley, S., Henderson, N., Towse, A. and Cole, A., 2022. *Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose?* [online] London: Office of Health Economics. Available at: https://www.ohe.org/publications/health-technology-assessment-gene-therapies-are-our-methods-fit-purpose. [Accessed 2 Sept. 2022].

Beswick, L., 2024. Chapter 11 - The health economics of cell and gene therapies. In: H.J. Federoff and R.A. Barker, eds, *Handbook of Clinical Neurology*, Cell and Gene Therapies for Neurologic Diseases. [online] Elsevier, pp.155—167. DOI: 10.1016/B978-0-323-90120-8.00004-6.

Bewersdorf, J.P., Patel, K.K., Shallis, R.M., Podoltsev, N.A., Kewan, T., Stempel, J., Mendez, L., Stahl, M., Stein, E.M., Huntington, S.F., Goshua, G. and Zeidan, A.M., 2024. Cost-effectiveness of adding quizartinib to induction chemotherapy for patients with FLT3-mutant acute myeloid leukemia. *Leukemia & Lymphoma*, 65(8), pp.1136—1144. DOI: 10.1080/10428194.2024.2344052.

Biddell, C.B., Kasow, K.A., Killela, M.K., Page, K.M., Wheeler, S.B., Drier, S.W., Kelly, M.S., Robles, J.M. and Spees, L.P., 2022. Understanding the financial and psychological impact of employment disruption among caregivers of pediatric HSCT recipients: a mixed methods analysis. *Supportive Care in Cancer*, 30(6), pp.4747—4757. DOI: 10.1007/s00520-022-06883-0.

Bloom, D. and Canning, D., 2003. Health as Human Capital and its Impact on Economic Performance. *The Geneva Papers on Risk and Insurance. Issues and Practice*, 28(2), pp.304—315.

Boateng-Kuffour, A., Skrobanski, H., Drahos, J., Kohli, P., Forster, K., Acaster, S., Pakbaz, Z., Li, N. and Williams, K., 2024. Appropriateness of the EQ-5D-5L in capturing health-related quality of life in individuals with transfusion-dependent β-thalassemia: a mixed methods study. *Health and Quality of Life Outcomes*, 22(1), p.54. DOI: 10.1186/s12955-024-02265-8.

Bona, K., Dussel, V., Orellana, L., Kang, T., Geyer, R., Feudtner, C. and Wolfe, J., 2014. Economic Impact of Advanced Pediatric Cancer on Families. *Journal of pain and symptom management*, 47(3), pp.594—603. DOI: 10.1016/j.jpainsymman.2013.04.003.

Boustani, M., Doty, E.G., Garrison, L.P., Smolen, L.J., Belger, M., Klein, T.M., Murphy, D.R., Burge, R., Wall, J.K. and Johnston, J.A., 2022. Assessing the Cost-effectiveness of a Hypothetical Disease-modifying Therapy With Limited Duration for the Treatment of Early Symptomatic Alzheimer Disease. *Clinical Therapeutics*, 44(11), pp.1449—1462. DOI: 10.1016/j.clinthera.2022.09.008.

Brouwer, W. and van Baal, P., 2023. Moving Forward with Taking a Societal Perspective: A Themed Issue on Productivity Costs, Consumption Costs and Informal Care Costs. *PharmacoEconomics*, 41(9), pp.1027—1030. DOI: 10.1007/s40273-023-01307-1.

Brown, P.A., Ji, L., Xu, X., Devidas, M., Hogan, L.E., Borowitz, M.J., Raetz, E.A., Zugmaier, G., Sharon, E., Bernhardt, M.B., Terezakis, S.A., Gore, L., Whitlock, J.A., Pulsipher, M.A., Hunger, S.P. and Loh, M.L., 2021a. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*, 325(9), pp.833—842. DOI: 10.1001/jama.2021.0669.

Brown, P.A., Shah, B., Advani, A., Aoun, P., Boyer, M.W., Burke, P.W., DeAngelo, D.J., Dinner, S., Fathi, A.T., Gauthier, J., Jain, N., Kirby, S., Liedtke, M., Litzow, M., Logan, A., Luger, S., Maness, L.J., Massaro, S., Mattison, R.J., et al., 2021b. Acute Lymphoblastic Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, 19(9), pp.1079—1109. DOI: 10.6004/jnccn.2021.0042.

Bryant, A.L., Walton, A.L., Shaw-Kokot, J., Mayer, D.K. and Reeve, B.B., 2015. Patient-Reported Symptoms and Quality of Life in Adults With Acute Leukemia: A Systematic Review. *Oncology nursing forum*, 42(2), pp.E91—E101. DOI: 10.1188/15.ONF.E91-E101.

Cancer Research UK, 2019. *Acute myeloid leukaemia (AML) incidence statistics*. [online] Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence. [Accessed 15 Nov. 2024].

Cancer Research UK, 2021. *Acute lymphoblastic leukaemia (ALL) incidence statistics*. [online] Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence. [Accessed 1 Apr. 2025].

Cappell, K.M. and Kochenderfer, J.N., 2023a. Long-term outcomes following CAR T cell therapy: what we know so far. *Nature Reviews. Clinical Oncology*, 20(6), pp.359—371. DOI: 10.1038/s41571-023-00754-1.

Cappell, K.M. and Kochenderfer, J.N., 2023b. Long-term outcomes following CAR T cell therapy: what we know so far. *Nature Reviews Clinical Oncology*, 20(6), pp.359—371. DOI: 10.1038/s41571-023-00754-1.

Carers UK, 2025. *Key facts and figures about caregiving*. [online] Carers UK. Available at: https://www.carersuk.org/policy-and-research/key-facts-and-figures/. [Accessed 4 Mar. 2025].

Carnall Farrar, 2024. *The Economic Impact of Dementia*. [online] Alzheimer's Society. Available at: https://www.alzheimers.org.uk/sites/default/files/2024-05/the-annual-costs-of-dementia.pdf.

CDA-AMC, 2021. *luspatercept | CDA-AMC*. [online] Available at: https://www.cda-amc.ca/luspatercept. [Accessed 2 Oct. 2024].

Cell and Gene Therapy Catapult, 2023. *Annual Review 2023: Accelerating growth in the advanced therapies industry*. [online] Available at: https://ct.catapult.org.uk/about/annual-review/2023. [Accessed 7 Feb. 2025].

Cell and Gene Therapy Catapult, 2024. *Cell and gene therapies*. [online] Available at: https://ct.catapult.org.uk/about/cell-and-gene-therapies. [Accessed 6 Dec. 2024].

Chen, Y., Bandosz, P., Stoye, G., Liu, Y., Wu, Y., Lobanov-Rostovsky, S., French, E., Kivimaki, M., Livingston, G., Liao, J. and Brunner, E.J., 2023. Dementia incidence trend in England and Wales, 2002—19, and projection for dementia burden to 2040: analysis of data from the English Longitudinal Study of Ageing. *The Lancet Public Health*, 8(11), pp.e859—e867. DOI: 10.1016/S2468-2667(23)00214-1.

Children with Cancer UK, 2025. *Acute Lymphoblastic Leukaemia (ALL)*. [online] Children with Cancer. Available at: http://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/leukaemia/acute-lymphoblastic-leukaemia/. [Accessed 28 Mar. 2025].

Chow, E.J., Simmons, J.H., Roth, C.L., Baker, K.S., Hoffmeister, P.A., Sanders, J.E. and Friedman, D.L., 2010. Increased cardiometabolic traits in pediatric survivors of acute lymphoblastic leukemia treated with total body irradiation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*, 16(12), pp.1674—1681. DOI: 10.1016/j.bbmt.2010.05.016.

Coyle, D. and Villeneuve, P.J.A., 2020. Economic Evaluation of Azacitidine in Elderly Patients with Acute Myeloid Leukemia with High Blast Counts. *PharmacoEconomics - Open*, 4(2), pp.297—305. DOI: 10.1007/s41669-019-00180-z.

CRUK, 2024. *CAR T-cell therapy*. [online] Available at: https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy. [Accessed 6 Dec. 2024].

Daver, N., Schlenk, R.F., Russell, N.H. and Levis, M.J., 2019. Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia*, 33(2), pp.299—312. DOI: 10.1038/s41375-018-0357-9.

Daver, N., Wei, A.H., Pollyea, D.A., Fathi, A.T., Vyas, P. and DiNardo, C.D., 2020. New directions for emerging therapies in acute myeloid leukemia: the next chapter. *Blood Cancer Journal*, 10(10), pp.1—12. DOI: 10.1038/s41408-020-00376-1.

Davis, M., O'Connell, T., Johnson, S., Cline, S., Merikle, E., Martenyi, F. and Simpson, K., 2018. Estimating Alzheimer's Disease Progression Rates from Normal Cognition Through Mild Cognitive Impairment and Stages of Dementia. *Current Alzheimer research*, 15(8), pp.777—788. DOI: 10.2174/1567205015666180119092427.

Deloitte, 2020. *The value of informal care in 2020*. Deloitte Access Economics.

Department for Work & Pensions, 2015. *Employment statistics for workers aged 50 and over, by 5-year age bands and gender*.

Department for Work & Pensions, 2024. *Get Britain Working White Paper*. [Policy paper] gov.uk. Available at: https://www.gov.uk/government/publications/get-britain-working-white-paper/get-britain-working-white-paper. [Accessed 6 Dec. 2024].

Department for Work and Pensions, 2023. *Employment Status of the Adult by Financial Year, Whether the Adult is an Informal Carer, Gender of the Adult and Age band of the Adult*.

Devlin, P.D.N., Parkin, D. and Janssen, B., 2020. An Introduction to EQ-5D Instruments and Their Applications. In: *Methods for Analysing and Reporting EQ-5D Data [Internet]*. [online] Springer. DOI: 10.1007/978-3-030-47622-9_1.

Döhner, H., Wei, A.H., Appelbaum, F.R., Craddock, C., DiNardo, C.D., Dombret, H., Ebert, B.L., Fenaux, P., Godley, L.A., Hasserjian, R.P., Larson, R.A., Levine, R.L., Miyazaki, Y., Niederwieser, D., Ossenkoppele, G., Röllig, C., Sierra, J., Stein, E.M., Tallman, M.S., et al., 2022. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*, 140(12), pp.1345—1377. DOI: 10.1182/blood.2022016867.

Dräger, J., Klein, M. and Sosu, E., 2024. The long-term consequences of early school absences for educational attainment and labour market outcomes. *British Educational Research Journal*, 50(4), pp.1636—1654. DOI: 10.1002/berj.3992.

Drummond, M.F., Neumann, P.J., Sullivan, S.D., Fricke, F.-U., Tunis, S., Dabbous, O. and Toumi, M., 2019. Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy. *Value in Health*, 22(6), pp.661—668. DOI: 10.1016/j.jval.2019.03.012.

El-Jawahri, A., Abel, G.A., Traeger, L., Waldman, L., Markovitz, N., VanDusen, H., Fathi, A., Steensma, D.P., LeBlanc, T.W., Horick, N.K., DeAngelo, D.J., Wadleigh, M., Hobbs, G., Foster, J., Brunner, A.M., Amrein, P., Stone, R.M., Temel, J.S. and Greer, J.A., 2019. Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy. *Leukemia*, 33(10), pp.2393—2402. DOI: 10.1038/s41375-019-0449-1.

EMA, 2017. *Advanced therapy medicinal products: Overview | European Medicines Agency (EMA)*. [online] Available at: https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview. [Accessed 10 Dec. 2024].

EMA, 2019. *Zynteglo | European Medicines Agency (EMA)*. [online] Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo. [Accessed 25 Mar. 2025].

EMA, 2022. *Aduhelm*. [online] Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/aduhelm. [Accessed 26 Mar. 2025].

FDA, 2021. FDA's Decision to Approve New Treatment for Alzheimer's Disease. *FDA*. [online] Available at: https://www.fda.gov/drugs/our-perspective/fdas-decision-approve-new-treatment-alzheimers-disease. [Accessed 27 Mar. 2025].

FDA, 2022. *ZYNTEGLO*. [online] FDA. Available at: https://www.fda.gov/vaccines-blood-biologics/zynteglo. [Accessed 25 Mar. 2025].

Firth, I., Schirrmacher, H., Zhang, K., Hampson, G. and Towse, A., 2021. *Exploring the financial sustainability of gene therapies*. [online] Office of Health Economics. Available at: https://www.ohe.org/wp-content/uploads/2021/05/Financial-Sustainability-of-Gene-Therapies-v2.pdf. [Accessed 7 Feb. 2025].

Fluchel, M.N., Kirchhoff, A.C., Bodson, J., Sweeney, C., Edwards, S.L., Ding, Q., Stoddard, G.J. and Kinney, A.Y., 2014. Geography and the Burden of Care in Pediatric Cancers. *Pediatric blood & cancer*, 61(11), pp.1918—1924. DOI: 10.1002/pbc.25170.

Fortune, E.E., Rogers, K., Lawrence, C., Saxton, C., Morris, V.G., LeBlanc, T.W., Sae-Hau, M. and Miller, M.F., 2023. Measuring Social Toxicity in Acute Myeloid Leukemia. *Blood*, 142(Supplement 1), p.5182. DOI: 10.1182/blood-2023-177783.

French, A.E., Tsangaris, E., Barrera, M., Guger, S., Brown, R., Urbach, S., Stephens, D. and Nathan, P.C., 2013. School Attendance in Childhood Cancer Survivors and Their Siblings. *The Journal of Pediatrics*, 162(1), pp.160—165. DOI: 10.1016/j.jpeds.2012.06.066.

Garas, A., McLean, L.A., De Luca, C.R., Downie, P. and McCarthy, M.C., 2019. Health-related quality of life in paediatric patients up to five years post-treatment completion for acute lymphoblastic leukaemia: a systematic review. *Supportive Care in Cancer*, 27(11), pp.4341—4351. DOI: 10.1007/s00520-019-04747-8.

Goldsmith, S.R., Ghobadi, A., Dipersio, J.F., Hill, B., Shadman, M. and Jain, T., 2022. CAR T versus HCT: An Evolving Perspective. *Transplantation and cellular therapy*, 28(11), pp.727—736. DOI: 10.1016/j.jtct.2022.07.015.

Green, C., Handels, R., Gustavsson, A., Wimo, A., Winblad, B., Sköldunger, A. and Jönsson, L., 2019. Assessing cost-effectiveness of early intervention in Alzheimer's disease: An open-source modeling framework. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 15(10), pp.1309—1321. DOI: 10.1016/j.jalz.2019.05.004.

Gustavsson, A., Brinck, P., Bergvall, N., Kolasa, K., Wimo, A., Winblad, B. and Jönsson, L., 2011. Predictors of costs of care in Alzheimer's disease: a multinational sample of 1222 patients. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 7(3), pp.318—327. DOI: 10.1016/j.jalz.2010.09.001.

Guy, G.P., Berkowitz, Z., Ekwueme, D.U., Rim, S.H. and Yabroff, K.R., 2016. Annual Economic Burden of Productivity Losses Among Adult Survivors of Childhood Cancers. *Pediatrics*, 138(Suppl 1), pp.S15—S21. DOI: 10.1542/peds.2015-4268D.

Haematological Malignancy Research Network (HMRN), 2024. *Survival statistics: Acute myeloid leukaemias*. [online] Available at: https://hmrn.org/statistics/survival. [Accessed 15 Nov. 2024].

Hampson, G., Towse, A. and Zhang, K., 2021. *Exploring the Financial Sustainability of Gene Therapies - OHE*. [online] OHE - Leading intellectual authority on global health economics. Available at: https://www.ohe.org/publications/exploring-financial-sustainability-gene-therapies/. [Accessed 21 Jan. 2025].

Harari, D., 2024. *Low growth: The economy's biggest challenge*. Research in brief: Quick reads for the 2024 Parliament. [online] House of Commons Library. Available at: https://commonslibrary.parliament.uk/low-growth-the-economys-biggest-challenge/. [Accessed 6 Dec. 2024].

Hayes, H., Darrow, B., Cookson, G., Cole, A. and Steuten, L., 2024. *Employer Costs from Respiratory Infections - OHE*. [online] OHE. Available at: https://www.ohe.org/publications/employer-costs-from-respiratory-infections/. [Accessed 4 Mar. 2025].

Henderson, N., Oyalo, P., Tunnicliffe, E., El Banhawi, H., Yen, S. and Hampson, G., 2025. *Challenges and Solutions for Budget Impact Analysis of Gene Therapies*. [OHE Contract Research] Available at: https://www.ohe.org/publications/challenges-and-solutions-for-budget-impact-analysis-of-gene-therapies/.

Hernlund, E., Svedbom, A., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E.V., Jönsson, B. and Kanis, J.A., 2013. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of Osteoporosis*, 8(1), p.136. DOI: 10.1007/s11657-013-0136-1.

Herring, W.L., Gould, I.G., Fillit, H., Lindgren, P., Forrestal, F., Thompson, R. and Pemberton-Ross, P., 2021. Predicted Lifetime Health Outcomes for Aducanumab in Patients with Early Alzheimer's Disease. *Neurology and Therapy*, 10(2), pp.919—940. DOI: 10.1007/s40120-021-00273-0.

Hippisley-Cox, J. and Coupland, C., 2009. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores | The BMJ. *BMJ*. [online] Available at: https://www.bmj.com/content/339/bmj.b4229. [Accessed 11 Feb. 2025].

HM Treasury, 2022. *The Green Book: appraisal and evaluation in central government*. [online] GOV.UK. Available at: https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-government. [Accessed 28 Aug. 2024].

Ho, J.K., Borle, K., Dragojlovic, N., Dhillon, M., Kitchin, V., Kopac, N., Ross, C. and Lynd, L.D., 2021. Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review. *PharmacoEconomics*, 39(9), pp.995—1019. DOI: 10.1007/s40273-021-01051-4.

Hogan, L.E., Brown, P.A., Ji, L., Xu, X., Devidas, M., Bhatla, T., Borowitz, M.J., Raetz, E.A., Carroll, A., Heerema, N.A., Zugmaier, G., Sharon, E., Bernhardt, M.B., Terezakis, S.A., Gore, L., Whitlock, J.A., Hunger, S.P. and Loh, M.L., 2023. Children's Oncology Group AALL1331:

Phase III Trial of Blinatumomab in Children, Adolescents, and Young Adults With Low-Risk B-Cell ALL in First Relapse. *Journal of Clinical Oncology*, 41(25), pp.4118—4129. DOI: 10.1200/JCO.22.02200.

Iyer, N.S., Balsamo, L.M., Bracken, M.B. and Kadan-Lottick, N.S., 2015. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. *Blood*, 126(3), pp.346—353. DOI: 10.1182/blood-2015-02-627414.

Jalkanen, K., Aarnio, E., Lavikainen, P., Jauhonen, H.-M., Enlund, H. and Martikainen, J., 2019. Impact of type 2 diabetes treated with non-insulin medication and number of diabetes-coexisting diseases on EQ-5D-5 L index scores in the Finnish population | Health and Quality of Life Outcomes | Full Text. *Health and Quality of Life Outcomes*, [online] 17. Available at: https://hqlo.biomedcentral.com/articles/10.1186/s12955-019-1187-9. [Accessed 11 Feb. 2025].

Jeha, S., Gaynon, P.S., Razzouk, B.I., Franklin, J., Kadota, R., Shen, V., Luchtman-Jones, L., Rytting, M., Bomgaars, L.R., Rheingold, S., Ritchey, K., Albano, E., Arceci, R.J., Goldman, S., Griffin, T., Altman, A., Gordon, B., Steinherz, L., Weitman, S., et al., 2006. Phase II Study of Clofarabine in Pediatric Patients With Refractory or Relapsed Acute Lymphoblastic Leukemia. *Journal of Clinical Oncology*, 24(12), pp.1917—1923. DOI: 10.1200/JCO.2005.03.8554.

Jobanputra, M., Paramore, C., Laird, S.G., McGahan, M. and Telfer, P., 2020. Co-morbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. *British Journal of Haematology*, 191(5), pp.897—905. DOI: 10.1111/bjh.17091.

Johannesson, M., Borgquis, L., Jönsson, B. and Råstam, L., 1991. The costs of treating hypertension — an analysis of different cut-off points. *Health Policy*, 18(2), pp.141—150. DOI: 10.1016/0168-8510(91)90095-F.

Johnson, P.C., Dhawale, T., Newcomb, R.A., Amonoo, H.L., Lavoie, M.W., Vaughn, D., Karpinski, K. and El-Jawahri, A., 2023. Longitudinal patient-reported outcomes in patients receiving chimeric antigen receptor T-cell therapy. *Blood Advances*, 7(14), pp.3541—3550. DOI: 10.1182/bloodadvances.2022009117.

Jones, K., Weatherly, H., Birch, S., Castelli, A. and Chalkley, M., 2024. *Unit Costs of Health and Social Care programme (2022 — 2027) | The new home for the Unit Costs of Health and Social Care report*. [online] Available at: https://www.pssru.ac.uk/unitcostsreport/. [Accessed 3 Mar. 2025].

Josten, E.J.C., Verbakel, E. and Boer, A.H. de, 2022. A longitudinal study on the consequences of the take-up of informal care on work hours, labour market exit and workplace absenteeism due to illness. *Ageing & Society*, 44(3), pp.495—518. DOI: 10.1017/S0144686X22000204.

Juliusson, G., Lehmann, S. and Lazarevic, V., 2021. Epidemiology and Etiology of AML. In: C. Röllig and G.J. Ossenkoppele, eds, *Acute Myeloid Leukemia*. [online] Cham: Springer International Publishing, pp.1—22. DOI: 10.1007/978-3-030-72676-8_1.

Kansal, A.R., Reifsnider, O.S., Brand, S.B., Hawkins, N., Coughlan, A., Li, S., Cragin, L., Paramore, C., Dietz, A.C. and Caro, J.J., 2021. Economic evaluation of betibeglogene autotemcel (Beti-cel) gene addition therapy in transfusion-dependent β-thalassemia. *Journal of Market Access & Health Policy*, [online] 9(1). DOI: 10.1080/20016689.2021.1922028.

Kantarjian, H., Kadia, T., DiNardo, C., Daver, N., Borthakur, G., Jabbour, E., Garcia-Manero, G., Konopleva, M. and Ravandi, F., 2021. Acute myeloid leukemia: current progress and future directions. *Blood Cancer Journal*, 11(2), pp.1—25. DOI: 10.1038/s41408-021-00425-3.

Karnon, J., Tolley, K., Vieira, J. and Chandiwana, D., 2012. Lifetime cost-utility analyses of deferasirox in beta-thalassaemia patients with chronic iron overload: a UK perspective. *Clinical Drug Investigation*, 32(12), pp.805—815. DOI: 10.1007/s40261-012-0008-2.

Kelkar, A.H., Antin, J.H. and Shapiro, R.M., 2023. Long-term health outcomes of allogeneic hematopoietic stem cell transplantation. *Frontiers in Oncology*, 13, p.1175794. DOI: 10.3389/fonc.2023.1175794.

Keller, E., Newman, J.E., Ortmann, A., Jorm, L.R. and Chambers, G.M., 2021. How Much Is a Human Life Worth? A Systematic Review. *Value in Health*, 24(10), pp.1531—1541. DOI: 10.1016/j.jval.2021.04.003.

Khan, R.B., Hudson, M.M., Ledet, D.S., Morris, E.B., Pui, C.-H., Howard, S.C., Krull, K.R., Hinds, P.S., Crom, D., Browne, E., Zhu, L., Rai, S., Srivastava, D. and Ness, K.K., 2014. Neurologic morbidity and quality of life in survivors of childhood acute lymphoblastic leukemia: a prospective cross-sectional study. *Journal of Cancer Survivorship*, 8(4), pp.688—696. DOI: 10.1007/s11764-014-0375-1.

Kieu, C. and Look, K.A., 2023. Cost-Effectiveness of a Hypothetical Gene Therapy for Alzheimer's Disease: A Markov Simulation Analysis. *Innovations in Pharmacy*, 14(3), p.10.24926/iip.v14i3.5500. DOI: 10.24926/iip.v14i3.5500.

Koneru, M., Arslan, S., Magalhaes-Silverman, M.M., Liu, H., Bejanyan, N., Di Stasi, A., McCallum, R., Quintero, S., Garrett, G., Wang, K., Smith, E., Shahim, T., Hoang, L., Crisostomo, J., Wilga-Savitski, A., Pickering, J., Angelo, L., Smith, A., Vera, J.F., et al., 2022. Early Results of MT-401 (Zedenoleucel) in Post-Transplant MRD+ aml Patients. *Blood*, 140(Supplement 1), pp.12718—12719. DOI: 10.1182/blood-2022-155602.

Koopmanschap, M., Burdorf, A. and Lötters, F., 2013. Work Absenteeism and Productivity Loss at Work. In: P. Loisel and J.R. Anema, eds, *Handbook of Work Disability: Prevention and Management*. [online] New York, NY: Springer, pp.31—41. DOI: 10.1007/978-1-4614-6214-9_3.

Korol, E.E., Wang, S., Johnston, K., Ravandi-Kashani, F., Levis, M. and Nooten, F. van, 2017. Health-Related Quality of Life of Patients with Acute Myeloid Leukemia: A Systematic Literature Review. *Oncology and Therapy*, 5(1), p.1. DOI: 10.1007/s40487-016-0039-6.

Krull, K.R., Brinkman, T.M., Li, C., Armstrong, G.T., Ness, K.K., Srivastava, D.K., Gurney, J.G., Kimberg, C., Krasin, M.J., Pui, C.-H., Robison, L.L. and Hudson, M.M., 2013. Neurocognitive Outcomes Decades After Treatment for Childhood Acute Lymphoblastic Leukemia: A Report From the St Jude Lifetime Cohort Study. *Journal of Clinical Oncology*, 31(35), pp.4407—4415. DOI: 10.1200/JCO.2012.48.2315.

Lexeo Therapeutics, 2023. *A 52-Week, Multicenter, Phase 1/2 Open-label Study to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease*. [Clinical trial registration] clinicaltrials.gov. Available at: https://clinicaltrials.gov/study/NCT03634007. [Accessed 11 Oct. 2024].

Li, N., Drahos, J., Boateng-Kuffour, A. and Calvert, M., 2022a. Health-Related Quality of Life and Disease Impacts in Adults with Transfusion-Dependent β-Thalassemia: Preliminary Results from the Global Longitudinal Survey | Blood | American Society of Hematology. *Blood*, [online] 140. DOI: https://doi.org/10.1182/blood-2022-162380.

Li, N., Drahos, J., Boateng-Kuffour, A., Calvert, M., Levine, L., Dongha, N., Pakbaz, Z., Oran, F.K., Iqbal, K., Shah, F. and Martin, A.P., 2022b. Health-Related Quality of Life and Disease Impacts in Adults with Transfusion-Dependent β-Thalassemia: Preliminary Results from the Global Longitudinal Survey. *Blood*, 140(Supplement 1), pp.10869—10870. DOI: 10.1182/blood-2022-162380.

Lin, J.K., Lerman, B.J., Barnes, J.I., Boursiquot, B.C., Tan, Y.J., Robinson, A.Q.L., Davis, K.L., Owens, D.K. and Goldhaber-Fiebert, J.D., 2018. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia. *Journal of Clinical Oncology*, 36(32), pp.3192—3202. DOI: 10.1200/JCO.2018.79.0642.

Lin, P.-J., D'Cruz, B., Leech, A.A., Neumann, P.J., Sanon Aigbogun, M., Oberdhan, D. and Lavelle, T.A., 2019. Family and Caregiver Spillover Effects in Cost-Utility Analyses of Alzheimer's Disease Interventions. *PharmacoEconomics*, 37(4), pp.597—608. DOI: 10.1007/s40273-019-00788-3.

Line, G.A., Whittington, M.D., Synnott, P.G., McKenna, A., Campbell, J., Pearson, S.D. and Rind, D.M., 2021. *Aducanumab for Alzheimer's Disease: Effectiveness and Value; Final Evidence Report and Meeting Summary.* [online] Institute for Clinical and Economic Review. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf.

Lloyd-Williams, H. and Hughes, D.A., 2021. A systematic review of economic evaluations of advanced therapy medicinal products. *British Journal of Clinical Pharmacology*, 87(6), pp.2428—2443. DOI: 10.1111/bcp.14275.

Lockwood, B., El-Jawahri, A., Walker, A.R., Russell, D., Gustin, J., Ehrman, S., Bose-Brill, S., Lustberg, M. and Bhatnagar, B., 2020. Psychological Distress in Young Adults with Acute Myeloid Leukemia Undergoing Induction Chemotherapy. *Blood*, 136, pp.17—18. DOI: 10.1182/blood-2020-140589.

Malard, F. and Mohty, M., 2020. Acute lymphoblastic leukaemia. *The Lancet*, 395(10230), pp.1146—1162. DOI: 10.1016/S0140-6736(19)33018-1.

Mallorie, S., 2024. *NHS Workforce Nutshell*. [online] The King's Fund. Available at: https://www.kingsfund.org.uk/insight-and-analysis/data-and-charts/nhs-workforce-nutshell. [Accessed 21 Jan. 2025].

Market Data Forecast ltd, 2025. *Gene Therapy Market Size, Growth & Forecast, 2033*. [online] Market Data Forecast. Available at: https://www.marketdataforecast.com/market-reports/gene-therapy-market. [Accessed 7 Feb. 2025].

Martins, R., Urbich, M., Brännvall, K., Gianinazzi, M., Ching, J.E., Khoury, C.P. and El-Hayek, Y.H., 2022. Modelling the Pan-European Economic Burden of Alzheimer's Disease. *JAR life*, 11, pp.38—46. DOI: 10.14283/jarlife.2022.7.

Matza, L.S., Paramore, L.C., Stewart, K.D., Karn, H., Jobanputra, M. and Dietz, A.C., 2020. Health state utilities associated with treatment for transfusion-dependent β-thalassemia. *The European journal of health economics: HEPAC: health economics in prevention and care*, 21(3), pp.397—407. DOI: 10.1007/s10198-019-01136-0.

Maude, S.L., Laetsch, T.W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., Bader, P., Verneris, M.R., Stefanski, H.E., Myers, G.D., Qayed, M., Moerloose, B.D., Hiramatsu, H., Schlis, K., Davis, K.L., Martin, P.L., Nemecek, E.R., Yanik, G.A., Peters, C., et al., 2018. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *New England Journal of Medicine*, 378(5), pp.439—448. DOI: 10.1056/NEJMoa1709866.

Mesterton, J., Wimo, A., By, A., Langworth, S., Winblad, B. and Jönsson, L., 2010. Cross sectional observational study on the societal costs of Alzheimer's disease. *Current Alzheimer Research*, 7(4), pp.358—367. DOI: 10.2174/156720510791162430.

Mody, R., Li, S., Dover, D.C., Sallan, S., Leisenring, W., Oeffinger, K.C., Yasui, Y., Robison, L.L. and Neglia, J.P., 2008. Twenty-five—year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*, 111(12), pp.5515—5523. DOI: 10.1182/blood-2007-10-117150.

Molenaar, R.J., Maciejewski, J.P., Wilmink, J.W. and van Noorden, C.J.F., 2018. Wild-type and mutated IDH1/2 enzymes and therapy responses. *Oncogene*, 37(15), pp.1949—1960. DOI: 10.1038/s41388-017-0077-z.

National organisation for rare disorders, 2024. *Acute Myeloid Leukemia*. [online] Available at: https://rarediseases.org/rare-diseases/acute-myeloid-leukemia/. [Accessed 15 Nov. 2024].

NHS, 2014. *National Haemoglobinopathy Registry Report 2013/14*. [online] Available at: https://nhr.mdsas.com/wp-content/uploads/2015/10/NHR_AnnualReport_2014.pdf.

NHS, 2018. *Alzheimer's disease - Treatment*. [online] nhs.uk. Available at: https://www.nhs.uk/conditions/alzheimers-disease/treatment/. [Accessed 5 Dec. 2024].

NHS, 2020. *National Haemoglobinopathy Registry Annual Report 2019/20*. [Annual data report 2019/20] Available at: https://nhr.mdsas.com/wpcontent/uploads/2021/01/2020_12_NHR_AnnualReport201920_Final.pdf.

NHS, 2022. *Thalassaemia - Treatment*. [online] nhs.uk. Available at: https://www.nhs.uk/conditions/thalassaemia/treatment/. [Accessed 12 Nov. 2024].

NHS, 2025a. *Build an NHS Fit For the Future*. [online] GOV.UK. Available at: https://www.gov.uk/missions/nhs. [Accessed 27 Feb. 2025].

NHS, 2025b. *Fit for the Future: The 10 Year Health Plan for England*. [online] Available at: https://assets.publishing.service.gov.uk/media/6866387fe6557c544c74db7a/fit-for-the-future-10-year-health-plan-for-england.pdf.

NHS England, 2022. *Sickle cell and thalassaemia screening: data report 2019 to 2020*. [online] GOV.UK. Available at: https://www.gov.uk/government/publications/sickle-cell-and-thalassaemia-screening-data-report-2019-to-2020/sickle-cell-and-thalassaemia-screening-data-report-2019-to-2020. [Accessed 9 Dec. 2024].

NHS England, 2023. *NHS England » NHS to offer stem cell transplants to cure life-limiting blood disorder*. [online] Available at: https://www.england.nhs.uk/2023/11/nhs-to-offer-stem-cell-transplants-to-cure-life-limiting-blood-disorder/. [Accessed 12 Nov. 2024].

NICE, 2017. *Midostaurin for untreated acute myeloid leukaemia: Committee Papers*. [online] Available at: https://www.nice.org.uk/guidance/ta523/documents/committee-papers-2.

NICE, 2019. *Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/TA567. [Accessed 25 Feb. 2025].

NICE, 2021a. *Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B cell acute lymphoblastic leukaemia in people 26 years and over: Committee*

Papers. [online] Available at: https://www.nice.org.uk/guidance/ta893/evidence/appraisal-consultation-committee-papers-pdf-13064338333.

NICE, 2021b. *Project information | Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968] | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/discontinued/gid-ta10334. [Accessed 25 Mar. 2025].

NICE, 2022. *Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. [Accessed 5 Jan. 2023].

NICE, 2023. *Potential issues and challenges in evaluation of disease-modifying dementia treatments*. HTA Innovation Laboratory Report.

NICE, 2024a. *1 Recommendations | Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/ta1003/chapter/1-Recommendations. [Accessed 26 Sept. 2024].

NICE, 2024b. *Overview | Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/ta1003. [Accessed 25 Feb. 2025].

NICE, 2024c. *Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years: Committee Papers*. [online] Available at: https://www.nice.org.uk/guidance/ta975/evidence/committee-papers-pdf-13426896925.

NICE, 2024d. *World's first gene editing therapy for blood disorder to be available to hundreds of patients in England*. [online] NICE. Available at: https://www.nice.org.uk/news/articles/worlds-first-gene-editing-therapy-for-blood-disorder-to-be-available-to-hundreds-of-patients-in-england. [Accessed 14 Oct. 2024].

NICE, 2025. *NICE approves groundbreaking one-off gene therapy for severe sickle cell disease*. [online] NICE website: The National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/news/articles/nice-approves-groundbreaking-one-off-gene-therapy-for-severe-sickle-cell-disease. [Accessed 25 Feb. 2025].

OBR, 2024. *Fiscal risks and sustainability*. [online] Office for Budget Responsibility. Available at: https://obr.uk/docs/dlm_uploads/Fiscal-risks-and-sustainability-report-September-2024-1.pdf.

O'Bryant, S.E., Waring, S.C., Cullum, C.M., Hall, J., Lacritz, L., Massman, P.J., Lupo, P.J., Reisch, J.S. and Doody, R., 2008. Staging Dementia Using Clinical Dementia Rating Scale Sum of Boxes Scores. *Archives of neurology*, 65(8), pp.1091—1095. DOI: 10.1001/archneur.65.8.1091.

Okamoto, Y., Nakazawa, Y., Inoue, M., Watanabe, K., Goto, H., Yoshida, N., Noguchi, M., Kikuta, A., Kato, K., Hashii, Y., Atsuta, Y. and Kato, M., 2020. Hematopoietic stem cell transplantation in children and adolescents with nonremission acute lymphoblastic leukemia. *Pediatric Blood & Cancer*, 67(12), p.e28732. DOI: 10.1002/pbc.28732.

ONS, 2022. *Employee earnings in the UK - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2022. [Accessed 23 Nov. 2023].

ONS, 2023a. *Rising ill-health and economic inactivity because of long-term sickness, UK - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/employmentandlabourmarket/peoplenotinwork/economicinactivity/articles/risingillhealthandeconomicinactivitybecauseoflongtermsicknessuk/2019to2023. [Accessed 19 Aug. 2024].

ONS, 2023b. *Unpaid care, England and Wales*. [online] Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/bulletins/unpaidcareenglandandwales/census2021. [Accessed 18 Mar. 2025].

ONS, 2024a. *Average hours worked and economic growth, UK - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/economy/grossdomesticproductgdp/articles/averagehoursworkedandeconomicgrowth/2024-01-22. [Accessed 22 Oct. 2024].

ONS, 2024b. *Employee earnings in the UK*. Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2024/relateddata?page=2. [Accessed 19 Mar. 2025].

ONS, 2024c. *Employee earnings in the UK - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2024. [Accessed 27 Feb. 2025].

ONS, 2024d. *Gross Domestic Product (GDP) - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/economy/grossdomesticproductgdp. [Accessed 9 Dec. 2024].

ONS, 2024e. *National life tables: UK - Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. [Accessed 11 Feb. 2025].

ONS, 2025. *Labour market statistics time series. Employment Rate 65+*. Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/timeseries/lfk6/lms. [Accessed 7 Mar. 2025].

Pagliaro, L., Chen, S.-J., Herranz, D., Mecucci, C., Harrison, C.J., Mullighan, C.G., Zhang, M., Chen, Z., Boissel, N., Winter, S.S. and Roti, G., 2024a. Acute lymphoblastic leukaemia. *Nature Reviews Disease Primers*, 10(1), pp.1—28. DOI: 10.1038/s41572-024-00525-x.

Pagliaro, L., Chen, S.-J., Herranz, D., Mecucci, C., Harrison, C.J., Mullighan, C.G., Zhang, M., Chen, Z., Boissel, N., Winter, S.S. and Roti, G., 2024b. Acute lymphoblastic leukaemia. *Nature Reviews Disease Primers*, 10(1), pp.1—28. DOI: 10.1038/s41572-024-00525-x.

Pandya, B.J., Young, C., Packnett, E.R., Xie, B., Lillehaugen, T., Block, A., Bernacki, K., Touya, M. and LeBlanc, T.W., 2024. Work absenteeism, disability, and lost wages among patients with acute myeloid leukemia and their caregivers: a cohort study using US administrative claims and productivity data. *Expert Review of Pharmacoeconomics & Outcomes Research*, 24(4), pp.521—532. DOI: 10.1080/14737167.2024.2311305.

Park, M., Jit, M. and Wu, J.T., 2018. Cost-benefit analysis of vaccination: a comparative analysis of eight approaches for valuing changes to mortality and morbidity risks. *BMC Medicine*, 16(1), p.139. DOI: 10.1186/s12916-018-1130-7.

Pepe, A., Meloni, A., Rossi, G., Midiri, M., Missere, M., Valeri, G., Sorrentino, F., D'Ascola, D.G., Spasiano, A., Filosa, A., Cuccia, L., Dello Iacono, N., Forni, G., Caruso, V., Maggio, A., Pitrolo, L., Peluso, A., De Marchi, D., Positano, V., et al., 2018. Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. *European Heart Journal. Cardiovascular Imaging*, 19(3), pp.299—309. DOI: 10.1093/ehjci/jex012.

Perry-Duxbury, M., Asaria, M., Lomas, J. and van Baal, P., 2020. Cured Today, Ill Tomorrow: A Method for Including Future Unrelated Medical Costs in Economic Evaluation in England and Wales. *Value in Health*, 23(8), pp.1027—1033. DOI: 10.1016/j.jval.2020.05.006.

Petersohn, S., Salles, G., Wang, M., Wu, J., Wade, S.W., Simons, C.L., Bennison, C., Siddiqi, R., Peng, W., Kloos, I., Castaigne, G. and Hess, G., 2022. Cost-effectiveness analysis of KTE-X19 CAR T therapy versus real-world standard of care in patients with relapsed/refractory mantle cell lymphoma post BTKi in England. *Journal of Medical Economics*, 25(1), pp.730—740. DOI: 10.1080/13696998.2022.2079317.

Petrou, P., 2023. Is it a chimera? A systematic review of the economic evaluations of CAR-T cell therapy - an update. *Expert Review of Pharmacoeconomics & Outcomes Research*, 23(6), pp.625—650. DOI: 10.1080/14737167.2023.2214731.

Phares, S., Trusheim, M., Emond, S.K. and Pearson, S.D., 2024. Managing the challenges of paying for gene therapy: strategies for market action and policy reform in the United States. *Journal of Comparative Effectiveness Research*, 13(12), p.e240118. DOI: 10.57264/cer-2024-0118.

Pike, J. and Grosse, S.D., 2018. Friction cost estimates of productivity costs in cost-of-illness studies in comparison with human capital estimates: a review. *Applied health economics and health policy*, 16(6), pp.765—778. DOI: 10.1007/s40258-018-0416-4.

Pinna Pintor, M., Fumagalli, E. and Suhrcke, M., 2024. The impact of health on labour market outcomes: A rapid systematic review. *Health Policy*, 143, p.105057. DOI: 10.1016/j.healthpol.2024.105057.

Potashman, M., Buessing, M., Levitchi Benea, M., Cummings, J., Borson, S., Pemberton-Ross, P. and Epstein, A.J., 2021. Estimating Progression Rates Across the Spectrum of Alzheimer's Disease for Amyloid-Positive Individuals Using National Alzheimer's Coordinating Center Data. *Neurology and Therapy*, 10(2), pp.941—953. DOI: 10.1007/s40120-021-00272-1.

Pui, C.-H., Yang, J.J., Hunger, S.P., Pieters, R., Schrappe, M., Biondi, A., Vora, A., Baruchel, A., Silverman, L.B., Schmiegelow, K., Escherich, G., Horibe, K., Benoit, Y.C.M., Izraeli, S., Yeoh, A.E.J., Liang, D.-C., Downing, J.R., Evans, W.E., Relling, M.V., et al., 2015. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 33(27), pp.2938—2948. DOI: 10.1200/JCO.2014.59.1636.

Pulte, D., Jansen, L., Gondos, A., Katalinic, A., Barnes, B., Ressing, M., Holleczek, B., Eberle, A. and Brenner, H., 2014. Survival of Adults with Acute Lymphoblastic Leukemia in Germany and the United States. *PLoS ONE*, 9(1), p.e85554. DOI: 10.1371/journal.pone.0085554.

Robinson, R.L., Rentz, D.M., Andrews, J.S., Zagar, A., Kim, Y., Bruemmer, V., Schwartz, R.L., Ye, W. and Fillit, H.M., 2020. Costs of Early Stage Alzheimer's Disease in the United States: Cross-Sectional Analysis of a Prospective Cohort Study (GERAS-US)1. *Journal of Alzheimer's disease: JAD*, 75(2), pp.437—450. DOI: 10.3233/JAD-191212.

Rocks, S., Issa, Z., Watt, T. and Rose Douglas, H., 2025. *Health care funding projections | The Health Foundation*. [online] Available at: https://www.health.org.uk/reports-and-analysis/working-papers/health-care-funding-projections. [Accessed 21 Jan. 2025].

Romei, V. and Smith, I., 2024. UK economy stalls in third quarter. *Financial Times*. [online] 15 Nov. Available at: https://www.ft.com/content/3a7d0c5c-81ba-4879-9289-5c94a120a1aa.

Russell-Smith, T.A., Brockbank, J., Mamolo, C. and Knight, C., 2021. Cost Effectiveness of Gemtuzumab Ozogamicin in the First-Line Treatment of Acute Myeloid Leukaemia in the UK. *PharmacoEconomics - Open*, 5(4), pp.677—691. DOI: 10.1007/s41669-021-00278-3.

Salzman, R., Cook, F., Hunt, T., Malech, H.L., Reilly, P., Foss-Campbell, B. and Barrett, D., 2018. Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments. *Molecular Therapy*, 26(12), pp.2717—2726. DOI: 10.1016/j.ymthe.2018.10.017.

Sampson, C., Subramaniyan, S., Napier, M., El Banhawi, H. and Hampson, G., 2025. *OHE cell and gene therapy health-related impacts template model*. Available at: https://github.com/Office-Health-Economics/CGT_template_model. [Accessed 1 Aug. 2025].

Sampson, C., Zamora, B., Watson, S., Cairns, J., Chalkidou, K., Cubi-Molla, P., Devlin, N., García-Lorenzo, B., Hughes, D.A., Leech, A.A. and Towse, A., 2022. Supply-Side Cost-Effectiveness Thresholds: Questions for Evidence-Based Policy. *Applied Health Economics and Health Policy*. [online] DOI: 10.1007/s40258-022-00730-3.

Santabárbara, J., Gracia-García, P., Pírez, G., López-Antón, R., De La Cámara, C., Ventura, T., Pérez-Sastre, M., Lobo, E., Saz, P., Marcos, G. and Lobo, A., 2016. Mortality in Mild Cognitive Impairment Diagnosed with DSM-5 Criteria and with Petersen's Criteria: A 17-Year Follow-Up in a Community Study. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, 24(11), pp.977—986. DOI: 10.1016/j.jagp.2016.07.005.

Sarkar, R.R., Gloude, N.J., Schiff, D. and Murphy, J.D., 2019. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *JNCI: Journal of the National Cancer Institute*, 111(7), pp.719—726. DOI: 10.1093/jnci/djy193.

Schultz, A.B., Chen, C.-Y. and Edington, D.W., 2009. The Cost and Impact of Health Conditions on Presenteeism to Employers. *PharmacoEconomics*, 27(5), pp.365—378. DOI: 10.2165/00019053-200927050-00002.

Schultz, A.B. and Edington, D.W., 2007. Employee health and presenteeism: a systematic review. *Journal of Occupational Rehabilitation*, 17(3), pp.547—579. DOI: 10.1007/s10926-007-9096-x.

Sendi, P. and Brouwer, W., 2004. Leisure time in economic evaluation: theoretical and practical considerations. *Expert Review of Pharmacoeconomics & Outcomes Research*, 4(1), pp.1—3. DOI: 10.1586/14737167.4.1.1.

Serrano-Pozo, A., Das, S. and Hyman, B.T., 2021. APOE and Alzheimer's Disease: Advances in Genetics, Pathophysiology, and Therapeutic Approaches. *The Lancet. Neurology*, 20(1), pp.68—80. DOI: 10.1016/S1474-4422(20)30412-9.

Shah, F., Telfer, P., Velangi, M., Pancham, S., Wynn, R., Pollard, S., Chalmers, E., Kell, J., Carter, A.M., Hickey, J., Paramore, C., Jobanputra, M. and Ryan, K., 2021. Routine management,

healthcare resource use and patient and carer-reported outcomes of patients with transfusion-dependent β-thalassaemia in the United Kingdom: A mixed methods observational study. *eJHaem*, 2(4), pp.738—749. DOI: 10.1002/jha2.282.

Shah, N.N., Tasian, S.K., Kohler, M.E., Hsieh, E.M., Baumeister, S.H.C., Summers, C., Shalabi, H., Pollard, J.A., Yates, B., Brazauskas, R., Ndifon, E., Yuan, C.M., Wang, H.-W., Kobusingye, H.K., Christianson, K., Weiss, A.A., Leckrone, E., Shaw, B.E., Auletta, J.J., et al., 2023. CD33 CAR T-Cells (CD33CART) for Children and Young Adults with Relapsed/Refractory AML: Dose-Escalation Results from a Phase I/II Multicenter Trial. *Blood*, 142(Supplement 1), p.771. DOI: 10.1182/blood-2023-179667.

Shalitin, S., Pertman, L., Yackobovitch-Gavan, M., Yaniv, I., Lebenthal, Y., Phillip, M. and Stein, J., 2018. Endocrine and Metabolic Disturbances in Survivors of Hematopoietic Stem Cell Transplantation in Childhood and Adolescence. *Hormone Research in Paediatrics*, 89(2), pp.108—121. DOI: 10.1159/000486034.

Sharma, A. and John, T.D., 2024. Dismantling cost and infrastructure barriers to equitable access to gene therapies for sickle cell disease. *The Lancet Haematology*, 11(8), pp.e556—e559. DOI: 10.1016/S2352-3026(24)00175-3.

Sharma, R., 2018. Health and economic growth: Evidence from dynamic panel data of 143 years. *PLOS ONE*, 13(10), p.e0204940. DOI: 10.1371/journal.pone.0204940.

Shouse, G., Danilov, A.V. and Artz, A., 2022. CAR T-Cell Therapy in the Older Person: Indications and Risks. *Current Oncology Reports*, 24(9), pp.1189—1199. DOI: 10.1007/s11912-022-01272-6.

Sittimart, M., Rattanavipapong, W., Mirelman, A.J., Hung, T.M., Dabak, S., Downey, L.E., Jit, M., Teerawattananon, Y. and Turner, H.C., 2024. An overview of the perspectives used in health economic evaluations. *Cost Effectiveness and Resource Allocation*, 22(1), p.41. DOI: 10.1186/s12962-024-00552-1.

von Stackelberg, A., Locatelli, F., Zugmaier, G., Handgretinger, R., Trippett, T.M., Rizzari, C., Bader, P., O'Brien, M.M., Brethon, B., Bhojwani, D., Schlegel, P.G., Borkhardt, A., Rheingold, S.R., Cooper, T.M., Zwaan, C.M., Barnette, P., Messina, C., Michel, G., DuBois, S.G., et al., 2016. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *Journal of Clinical Oncology*, 34(36), pp.4381—4389. DOI: 10.1200/JCO.2016.67.3301.

Staines, R., 2021. bluebird bio 'baffled' after NICE rejects beta-thalassaemia gene therapy. *pharmaphorum*. [online] 16 Feb. Available at: https://pharmaphorum.com/news/bluebird-bio-baffled-after-nice-rejects. [Accessed 25 Mar. 2025].

Sugden, R. and Williams, A.H., 1978. *The Principles of Practical Cost--Benefit Analysis*. Oxford: Oxford University Press.

Terwilliger, T. and Abdul-Hay, M., 2017. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer Journal*, 7(6), pp.e577—e577. DOI: 10.1038/bcj.2017.53.

Thalassaemia Internation Federation, 2021. *2021 Guidelines for the management of transfusion dependent thalassaemia (TDT).* [online] pp.574—574. Available at: http://tidsskriftet.no/article/3309820. [Accessed 12 Nov. 2024].

Thol, F. and Heuser, M., 2021. Treatment for Relapsed/Refractory Acute Myeloid Leukemia. *HemaSphere*, 5(6), p.e572. DOI: 10.1097/HS9.0000000000000572.

Touchon, J., Lachaine, J., Beauchemin, C., Granghaud, A., Rive, B. and Bineau, S., 2014. The impact of memantine in combination with acetylcholinesterase inhibitors on admission of patients with Alzheimer's disease to nursing homes: cost-effectiveness analysis in France. *The European Journal of Health Economics*, 15(8), pp.791—800. DOI: 10.1007/s10198-013-0523-y.

Tremblay, G., Dolph, M., Patel, S., Brandt, P. and Forsythe, A., 2018. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. *Cost Effectiveness and Resource Allocation*, 16(1), p.33. DOI: 10.1186/s12962-018-0153-4.

Tsochatzis, E.A., Bosch, J. and Burroughs, A.K., 2014. Liver cirrhosis. *Lancet (London, England)*, 383(9930), pp.1749—1761. DOI: 10.1016/S0140-6736(14)60121-5.

Udeze, C., Fang, H., Ogunsile, F.J., Mujumdar, U., Nie, X., Yang, H., Jeyakumar, S., Li, N., Zhao, J. and Lopez, A., 2023. P2 Economic Evaluation of Exagamglogene Autotemcel (EXA-CEL) Gene-Edited Therapy in Patients with Transfusion-Dependent Beta-Thalassemia. *Value in Health*, 26(6), p.S1. DOI: 10.1016/j.jval.2023.03.015.

Vakiti, A., Reynolds, S.B. and Mewawalla, P., 2024. Acute Myeloid Leukemia. In: *StatPearls*. [online] Treasure Island (FL): StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/books/NBK507875/. [Accessed 15 Nov. 2024].

Verbooy, K., Hoefman, R., Exel, J. van and Brouwer, W., 2018. Time Is Money: Investigating the Value of Leisure Time and Unpaid Work. *Value in Health*, 21(12), pp.1428—1436. DOI: 10.1016/j.jval.2018.04.1828.

Vetsch, J., Wakefield, C.E., Robertson, E.G., Trahair, T.N., Mateos, M.K., Grootenhuis, M., Marshall, G.M., Cohn, R.J. and Fardell, J.E., 2018. Health-related quality of life of survivors of childhood acute lymphoblastic leukemia: a systematic review. *Quality of Life Research*, 27(6), pp.1431—1443. DOI: 10.1007/s11136-018-1788-5.

Wagner, T.D., Buelt, L., Westrich, K. and Campbell, J.D., 2024. Improving access to gene therapies: a holistic view of current challenges and future policy solutions in the United States. *Journal of Comparative Effectiveness Research*, 13(12), p.e240098. DOI: 10.57264/cer-2024-0098.

Walker, S., Griffin, S., Asaria, M., Tsuchiya, A. and Sculpher, M., 2019. Striving for a Societal Perspective: A Framework for Economic Evaluations When Costs and Effects Fall on Multiple Sectors and Decision Makers. *Applied Health Economics and Health Policy*, 17(5), pp.577—590. DOI: 10.1007/s40258-019-00481-8.

Watt, T., Raymond, A., Rachet-Jacquet, L., Head, A., Kypridemos, C., Kelly, E. and Charlesworth, A., 2023. *Health in 2040: projected patterns of illness in England | The Health Foundation*. [online] Available at: https://www.health.org.uk/reports-and-analysis/reports/health-in-2040-projected-patterns-of-illness-in-england. [Accessed 21 Jan. 2025].

Weidlich, D., Kefalas, P. and Guest, J.F., 2016. Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom. *Transfusion*, 56(5), pp.1038—1045. DOI: 10.1111/trf.13513.

Whittington, M.D., Campbell, J.D., Rind, D., Fluetsch, N., Lin, G.A. and Pearson, S.D., 2022. Cost-Effectiveness and Value-Based Pricing of Aducanumab for Patients With Early Alzheimer Disease. *Neurology*, [online] 98(9). DOI: 10.1212/WNL.0000000000013314.

Wimo, A., Reed, C.C., Dodel, R., Belger, M., Jones, R.W., Happich, M., Argimon, J.M., Bruno, G., Novick, D., Vellas, B. and Haro, J.M., 2013. The GERAS Study: A Prospective Observational Study of Costs and Resource Use in Community Dwellers with Alzheimer's Disease in Three European Countries — Study Design and Baseline Findings. *Journal of Alzheimer's Disease*, 36(2), pp.385—399. DOI: 10.3233/JAD-122392.

Wittenberg, R., Knapp, M., Hu, B., Comas-Herrera, A., King, D., Rehill, A., Shi, C., Banerjee, S., Patel, A., Jagger, C. and Kingston, A., 2019. The costs of dementia in England. *International Journal of Geriatric Psychiatry*, 34(7), p.1095. DOI: 10.1002/gps.5113.

Wong, C.H., Li, D., Wang, N., Gruber, J., Lo, A.W. and Conti, R.M., 2023. The estimated annual financial impact of gene therapy in the United States. *Gene Therapy*, 30(10), pp.761—773. DOI: 10.1038/s41434-023-00419-9.

Wood, M. and Bosch, I., 2022. *From safety net to springboard: putting health at the heart of economic growth*. [online] NHS Confederation. Available at: https://www.nhsconfed.org/system/files/2022-10/From-safety-net-to-springboard_0.pdf. [Accessed 7 Feb. 2025].

Wouterse, B., van Baal, P., Versteegh, M. and Brouwer, W., 2023. The Value of Health in a Cost-Effectiveness Analysis: Theory Versus Practice. *PharmacoEconomics*, 41(6), pp.607—617. DOI: 10.1007/s40273-023-01265-8.

Zhang, N., Wu, J., Wang, Q., Liang, Y., Li, X., Chen, G., Ma, L., Liu, X. and Zhou, F., 2023. Global burden of hematologic malignancies and evolution patterns over the past 30 years. *Blood Cancer Journal*, 13(1), p.82. DOI: 10.1038/s41408-023-00853-3.

Zheng, Z., Yabroff, K.R., Guy, G.P., Han, X., Li, C., Banegas, M.P., Ekwueme, D.U. and Jemal, A., 2015. Annual Medical Expenditure and Productivity Loss Among Colorectal, Female Breast, and Prostate Cancer Survivors in the United States. *JNCI Journal of the National Cancer Institute*, 108(5), p.djv382. DOI: 10.1093/jnci/djv382.

Appendix

A. Methodology

This section outlines a generalisable methodology for our analysis, aligned with the rationale and approach described above. It is designed to be taken as a protocol for modelling the value of CGTs in any disease area. We outline generalisable methods for structuring disease models, identifying parameters, and specifying the analysis. The informativeness of our approach relies on meaningful selection of disease areas, and so we outline a rational methodology for selecting indications.

A template model, based on the model protocol outlined below, was developed in R and is available open-source (Sampson et al., 2025). This aligns with our aim to develop a generalisable approach to modelling outcomes that can be applied and adapted to different therapeutic areas or types of technology. Its usefulness, in its current form, relies on the use of a cohort state transition model described in the model structure section below.

As an open-source model, adaptations can be made to the R script to more accurately model outcomes as required. This has been necessary in making the template more applicable to the specific case studies we have modelled. For example, to facilitate accurate representation of clinical pathways and treatment protocols for CGTs (in Alzheimer's disease), our model incorporates functionality for the specification of states with fixed durations. These adaptations are present in the current template.

The process of selecting a set of indications is informed by a qualitative assessment of the likelihood of CGTs emerging in the near future, the feasibility of modelling the indication, and the extent of disease burden, as described in section 4.

Modelling protocol

Model structure

We develop disease-specific decision models informed by published economic evaluations and appraisals identified through targeted literature reviews. As far as possible, model structures should align with those used in previously validated or tested decision models.

Our methodology seeks to facilitate interpretation of the value of CGTs across disease areas. We therefore prioritise consistency in the model structures. In particular, all models adopt a cohort state transition structure, with states specified on the basis of disease state. Cohort state transition models simulate a group's movement (often progression) through a mutually exclusive and collectively exhaustive set of disease states. The amount of time spent in each state will determine the relevant outcomes for the cohort. The use of a cohort means that the model does not consider differences between individuals and seeks to provide accurate estimates of outcomes on average. CGTs seek to substantially alter disease progression, such that model results are expected to be less reliant on a nuanced specification of the model structure, or precision in the definition of health states and transitions.

The identification of health states is determined based on current treatment pathways for selected indications in the UK, accounting for any precedent in the evaluation of cell and gene therapeutic options. The models should be parsimonious, built with as few health

states as is necessary, to support generalisability. The feasibility of transitions (between given states) should reflect realistic disease trajectories, and different indications will require different levels of complexity in this regard.

The models seek to capture meaningful differences in patient disease history and treatment effects. Given this, elements of the model structure are expected to differ between the models, including cycle length, treatment waning, mortality risks, and any assumptions taken to capture long-term outcomes. This should be determined based on targeted or systematic literature reviews of the disease area. To facilitate accurate representation of clinical pathways and treatment protocols for CGTs, our model incorporates functionality for the specification of states with fixed durations.

Table 13 outlines the parameters required for a state transition model, accompanied by a description of each parameter.

Table 13 State transition model parameters

PARAMETER	DESCRIPTION
States (S)	Health states in the model that patients can occupy
Transition probabilities (P_{ij})	The probability of moving between states, i and j
Cycle length (Δt)	The duration of one model cycle (e.g., 1 month, 1 year).
Time horizon (T)	The total duration of the model (e.g. 10 years, 20 years)
Health state distribution (N_t)	The distribution of the population across health states at time, t

A state transition model consists of discrete health states ($S_1, S_2, \ldots, S_n$) where n is the number of health states. A simple example would be:

- S_1 = Healthy
- S_2 = Diseased
- S_3 = Dead

Each model has a series of transition probabilities, which is the probability, P_{ij}, of moving from the health state i to j. These probabilities can be represented in a transition matrix (P), an example is displayed below:

$$P = \begin{bmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{bmatrix}$$

The number of individuals that occupy each state over time is calculated iteratively, depending on the cycle length, Δt, for the full duration of the time horizon T. This calculation occurs using the following formula:

$$N_t = N_{t-1}P$$

Where N_t is the distribution of patients at time t, N_{t-1} is the distribution on the previous cycle, and P is the transition matrix.

The outcomes associated with occupancy of each state are then calculated. The transition probabilities, and the initial state distribution (N_0) may differ depending on the treatment offered to patients, hence driving the differences in outcomes.

Parameters

Key input parameters to the model include probabilities for transitions between states, state-based estimates of outcomes, and population characteristics. These should all be derived from published literature, clinical trial data, or appraisals of relevant technologies.

Parameters should be selected based on their alignment with the population, intervention, and outcomes specified in our approach. As far as possible, evidence should be derived in the UK setting, or from comparable health services.

Both transition probabilities and state-based outcomes may differ between the CGT and SoC. However, we assume that CGTs are disease modifying, and that their effectiveness can therefore be reflected in differential estimates of disease progression (transition probabilities).

Future unrelated medical costs are incorporated using standard methods described in the literature and are applied equivalently across scenarios. We use estimates from Asaria et al. (2017), inflated to 2024 prices. The model multiplies person-time alive in each cycle with age-specific per-capita spend, and is included in the systems cost category.

Analytic methods

Table 14 summarises the key analytic configuration of our models in the base case, accompanied by the NICE reference case specification for comparison.

Table 14 **Model settings**

PARAMETER	BASE CASE	NICE REFERENCE CASE (NICE, 2022)
Perspective	Society	NHS/PSS
Time horizon	10 years	Lifetime
Discount rate costs	0%	3.5%
Discount rate health benefits (SLY, QALYs)	0%	3.5%
Value of health outcomes: QALY	£70,000	£20,000-£30,000

SLY = statistical life year; QALY = quality adjusted life year

Time horizon

The time horizon for our analysis is the duration over which the cohort is modelled and outcomes are observed. It should be specified based on what is informative to the decision-maker. As a guideline, the UK Green Book suggests a time horizon of 10 years as "a suitable working assumption for many interventions".

However, the Green Book advises that the time horizon should be long enough to capture all significant costs and benefits associated with the interventions' useful lifespan. Interventions likely to have longer term effects, for example vaccination programmes or infrastructure projects with significant long-term costs or benefits, may require evaluation periods extending several decades into the future (e.g. 60-years), or even a lifetime horizon. A complexity in our analysis is that the evaluation of a CGT 'system-shift' does not have an obvious, predictable, or measurable lifespan.

According to NICE guidance, a lifetime horizon is justifiable when a technology leads to differences in patient survival or benefits that persist for the remainder of their life (NICE, 2022). However, lifetime time horizons are associated with high levels of uncertainty given the assumptions required to extrapolate data on disease progression and outcomes beyond available real-world evidence.

Our analysis encompasses a range of indications with different ages of onset/treatment initiation and varying disease progression rates, and therapies with various mechanisms of action (i.e. extending life vs. improving quality of life). Accordingly, a unified fixed time horizon must strike a balance between capturing treatment costs and benefits across indications, data limitations, and contextual considerations.

A 10-year time horizon may capture some changes in long term treatment outcomes and limit uncertainty, while aligning with the healthcare planning and budgetary considerations the UK, e.g. the NHS 10-year 'long term plan' (NHS, 2025a). Additional longer fixed time horizons (e.g. 20 and 30 years) could be presented where relevant (Drummond et al., 2019). Since it's expected that CGTs will have long-lasting and sustained effects over a patient's life course, estimating the longer-term outcomes is likely to have important implications for the analysis.

For all of our indications, we also present an annual 'steady-state' time horizon, in which outcomes are evaluated once the system has stabilised, i.e. there is a consistent number of new patients entering the model and dying each year. A steady-state model examines costs and outcomes for a single, typical year in a stable population. In practice, the model is run until all new patients have died (e.g. 100 years), and then that year is taken as representative. Thus, the analysis focuses on newly incident (future) patients and excludes the gains associated with treating a stock of prevalent patients with unmet needs. This approach is used to estimate the annual impact of a policy or intervention and can be scaled to any number of years. It estimates the ongoing costs and benefits after full implementation of an intervention (in our case, a system-shift), rather than the transitional effects of introducing a new intervention.

Discount rates

Technology appraisals and evaluations of investment decisions typically employ discounting. This is based on the notion of 'net present value' and the idea that the value of costs and benefits is diminished as they move further into the future. People — and governments — prefer to realise benefits sooner rather than later, and to defer costs or burdens into the future. However, the realisation of a CGT system-shift will require ongoing investment of currently unknown timing and magnitude, and the definition of 'present' — for the identification of net present value — is currently unspecified. This is particularly challenging when our analysis considers future (newly incident) patients, who cannot be treated at present but whose outcomes would be diminished in value through the application of discounting. Therefore, to simplify interpretation of the results, and to avoid difficult ethical justifications for the deprioritisation of future populations, our base case analysis adopts a 0% discount rate.

Scenarios

As outlined in our approach, we model two alternative scenarios when estimating the potential benefits of CGTs, a 'most credible' scenario A and a more optimistic scenario B. For disease areas in which there is a treatment in the pipeline, this facilitates consideration of uncertainties in where the CGT will fit in the patient pathway, who may be eligible, and its effectiveness. In contrast, where CGTs are already approved and available in the market, it provides an estimate if, say, there were to be an improvement in the effectiveness of treatments, a change in placement in the patient pathway, or an expansion in the eligibility of patients.

For each scenario, the overall approach and execution of the model will remain consistent, with differences being specified as alternative parameter inputs. Full results will be presented for each scenario for each case study.

Valuation of outcomes

Our analyses estimate the monetised value of outcomes within each of the individuals (micro), systems (meso), and national economy (macro) categories described above. Outcomes may be positive or negative, but our focus in these analyses is on the incremental monetised value of outcomes associated with a CGT system-shift.

The way that outcomes are valued — monetarily — is critical to the analysis and requires careful interpretation. Simply summing the individual benefits, national economy benefits, and health and social system benefits, and attributing this value as a macroeconomic benefit would result in double-counting. For example, if we were to sum the improved mortality using the value of a quality-adjusted life year (QALY), based on the Green Book valuation, together with productivity costs using the human capital approach (HCA), there would be an overlap in the benefits considered. Here, we describe how health and productivity should be valued in this analysis.

Health

In the valuation of health benefits, we follow the Green Book approach to the measurement and valuation of risks to life and health (HM Treasury, 2022). The measurement of health impact can be expressed in terms of both the length of life (life years gained) and quality of life (QoL).

A statistical life year (SLY) represents an additional year of life, and its valuation depends on the age of the individual benefitting from the intervention; a higher value is placed on the life of a child than on that of an elderly person (Keller et al., 2021). The measurement reflects only the length of life dimension.

A QALY represents a year of life in perfect health, accounting for both the length of life and quality of life (QoL), see the equation below. The QoL element is often estimated using the EQ-5D, which is a tool recommended by NICE and used to show the changes in self-reported health over time or relative to the receipt of a healthcare intervention. In this case, health-related QoL is described using five dimensions: mobility, ability to self-care, ability to carry out usual activities, pain/discomfort, and anxiety/depression (Devlin, Parkin and Janssen, 2020). Where possible, we use QoL values derived using the EQ-5D. Below are a series of equations to show how QALY gains are calculated in our analysis, with Table 15 outlining the key parameters.

Table 15 Health outcomes parameters

PARAMETER	DESCRIPTION
Life years (L_t)	The number of life years in any year (t)
Health related QoL (U_t)	The health-related quality of life in any year (t)
Discount rate (r)	The rate at which outcomes accrued after the first year are discounted each year
Time horizon (T)	The total duration of the model (e.g. 10 years, 20 years)

$$QALY_t = L_t \times U_t$$

For both the CGT and SoC, we calculate the total QALYs across the entire population (incident and prevalent).

$$QALY_{SOC} = \sum_{t=1}^{T} (\frac{L_t^{SOC} \times U_t^{SOC}}{(1+r)^t}$$

$$QALY_{CGT} = \sum_{t=1}^{T} (\frac{L_t^{CGT} \times U_t^{CGT}}{(1+r)^t}$$

$$\Delta QALY = QALY_{CGT} - QALY_{SOC}$$

We then monetise the QALYs or SLYs, both the difference in incremental health outcomes and the absolute gains for CGT and SoC. The monetary valuations we apply are from the Green Book and are based on representative samples of the population, who differ based on incomes, preferences, age, states of health, and other circumstances. Their values are comparable and represent the 'social value' that society places on either an improvement in life expectancy and QoL, the QALY, or a small change in the probability of gaining/losing a year of life expectancy, the SLY (HM Treasury, 2022).

Ultimately, whether SLYs or QALYs should be used depends upon the expected impact of the CGT intervention. If both length of life and quality of life are improved, the QALY would be the most appropriate measure to use.

Table 16 provides the monetary values of the QALY and SLY in the Green Book (HM Treasury, 2022).

Table 16 Valuation of health benefits

PARAMETER	VALUE	(SOURCE)
Monetary value of a QALY (V_{QALY})	£70,000/QALY (20/21 prices)	(HM Treasury, 2022)
Monetary value of a SLY (V_{SLY})	£60,000/SLY	(HM Treasury, 2022)

In contrast to these values, when evaluating health technologies, NICE applies a threshold of £20,000-£30,000 per QALY when considering its cost-effectiveness to the NHS (NICE, 2022). An intervention is deemed good value for money for the NHS if its associated cost per QALY falls within or below this range. NICE's cost-effectiveness threshold is not intended as a measure of the value of a QALY, but rather of the marginal cost of generating a QALY in the NHS (Sampson et al., 2022).

Time use

Different uses of time for patients and carers can generate differential value. We categorise and value patient and carer time use as either relating to individuals, systems, or the national economy. This approach allows flexibility in the valuation of different time-use inputs, as they relate to different treatment indications and populations. We anticipate that the best evidence will be available for differences in time spent in paid employment, which generates value for the national economy. We may also identify evidence for productivity impacts realised at the systems level, for example where formal care funded by NHS and social care services is displaced by informal caregiving by patients. Some changes in time use will only give rise to differential value at the individual level, such as changes in leisure time.

We estimate and value time as a proportion of all of a person's time. For working time, we standardise time-use calculations as full-time equivalents (FTEs), representing the proportion of a full-time workload impacted by illness or caregiving responsibilities. For example, if we assume an average full-time schedule of 40 hours per week, and a person loses 10 hours of work per week due to illness, this implies a loss of 0.25 FTE.

Estimates of time based on FTEs are converted in our analysis to a proportion of all of a person's time (on average), which can be expressed as a function of FTEs:

$$P_{(all)} = \frac{t}{T} \times FTE \times P_{(FTE)}$$

Where t is the number of hours associated with an FTE, T is the total available hours, FTE is the (average) number of FTEs per patient (e.g. based on the proportion of people in work) and $P_{(FTE)}$ is the FTE productivity loss associated with illness for those in work (based on estimates of absenteeism and presenteeism). For example, we can calculate a $P_{(all)}$ for a patient population where 80% of the patients work a 38-hour week and lose 0.5 FTEs due to illness:

$$P_{(all)} = \frac{38}{168} \times 0.8 \times 0.5 \ = 0.0905$$

Thus, the proportion of total weekly time impacted is 9.05%, which equates to 15.2 hours per week. This method ensures that productivity gains and losses are appropriately scaled relative to total available time, allowing for a consistent estimate of economic impact.

National economy

Productivity gains/losses at the macro level, due to changes in productivity and employment rates, are adjusted using FTE-weighted time loss due to absenteeism and presenteeism. Estimates are made in terms of the costs related to absenteeism, i.e. days of work lost during illness, due to both mortality and morbidity. Productivity impacts associated with family members' and informal caregivers' time use is estimated equivalently. The proportion of impacted time for patients and carers is valued based on the average income in the UK, obtained from the most recent estimates from the Office for National Statistics (ONS) (ONS, 2022).

For patients, the impact of mortality on productivity may be estimated using either the human capital approach (HCA) or the friction cost approach (FCA). The HCA calculates the economic loss due to illness, disability, or death by estimating the lost earnings that would have been generated by the individual over their remaining working life. The FCA only accounts for productivity losses in the 'friction period', or the time it takes to find and train a replacement worker who can perform the job at the same level as the person who is deceased or otherwise unable to work. The FCA includes costs associated with finding, hiring, and training a replacement worker, and any temporary loss of productivity during this transition period.

There is a lack of consensus over which approach is best to quantify formal market productivity losses (Pike and Grosse, 2018). The friction cost approach likely underestimates the long-term impact of mortality; however, the HCA likely overestimates these productivity losses. HCA better represents the loss of productive potential of individuals due to ill health and death, whereas the FCA only accounts for a short-term impact on the economy. The difference between HCA and FCA estimates differs widely across studies (Pike and Grosse, 2018), and will ultimately depend on the impact of the intervention and the age of the population affected. In this analysis, losses will be estimated using the HCA as this may better reflect a societal perspective with a long time horizon.

Systems

Similarly, for meso productivity gains/losses, we adjust informal caregiving time by FTE to estimate its displacement of formal care services. The valuation of informal care is at the same rate as formal workplace productivity impacts, assuming that the value of unpaid labour is equivalent to that of paid labour (Park, Jit and Wu, 2018; Deloitte, 2020). Patient time savings among patients who are informal caregivers', represented in FTE units, allow us to estimate sector-level cost reductions within the NHS and social care systems.

Individuals

'Micro' productivity gains/losses can be difficult to conceptualise and measure, given that time use on an individual level reflects reallocation of time to alternative purposes (which can be more or less 'valuable'), and not time 'lost.' There is a lack of consensus on how to best value "unproductive" leisure time. The ideal approach would consistently capture and value leisure time while not double-counting (Sendi and Brouwer, 2004). The opportunity cost method can be used for valuing leisure time in terms of monetary costs, utilising a fraction (or multiple) of the wage rate based on the context and methodology (Verbooy et al., 2018). This assumes that individuals, given limited time, choose a combination of work and leisure time that maximises their utility (Sendi and Brouwer, 2004). Another approach is to capture leisure time in terms of quality of life, as measured by health state valuations. However, quality of life instruments may not be explicit in this respect and may not fully capture the impact of illness on an individual's ability to enjoy leisure time (Sendi and Brouwer, 2004). For this reason, we include 'micro' productivity impacts when loss of leisure time is likely not fully captured by health state valuations, and where data on explicit time loss and suitable proxies for valuation are available. For example, not all informal caregivers are formally employed (thus not contributing to 'macro' productivity value), but their caregiving time 'loss' may be explicitly documented. Thus, for our analysis we value caregiving time among unemployed informal caregivers as lost leisure time where appropriate.

Our approach enables a breakdown of productivity value in terms of to whom they accrue: the national economy, systems (e.g. health and social care), and individuals (e.g. patients and their carers), while preventing double-counting.

B. Acute lymphoblastic leukaemia details

Acute lymphoblastic leukaemia (ALL) is an aggressive haematological malignancy characterised by the clonal proliferation of immature lymphoid cells, known as lymphoblasts, in the bone marrow and peripheral blood. This uncontrolled proliferation impairs normal blood cell production, leading to a range of clinical symptoms (Terwilliger and Abdul-Hay, 2017). ALL is most prevalent in children, although it can also affect adults, particularly those over 40 years of age. Leukaemia is the most prevalent childhood cancer in the UK and ALL is the predominant form of childhood leukaemia, accounting for about 78% of all leukaemia diagnoses in children in the UK (Children with Cancer UK, 2025).

ALL arises from mutations in the haematopoietic stem cells that result in the accumulation of lymphoblasts. These abnormal cells interfere with normal haematopoiesis, causing the ineffective production of red blood cells, white blood cells, and platelets. As a result, patients present with symptoms of anaemia, neutropenia, and thrombocytopenia. The disease can also infiltrate extramedullary sites such as the liver, spleen, and central nervous system (CNS), leading to more severe manifestations (Terwilliger and Abdul-Hay, 2017).

Globally, over 150,000 new cases of ALL and over 40,000 deaths due to ALL were reported in 2019 (Zhang et al., 2023). Incidence in the US was estimated at 1.8 per 100,000 people in 2021, with age-specific rates highest in children aged 1—4 years (Pagliaro et al., 2024b). In the UK, ALL is responsible for 765 new cases of leukaemia each year (Cancer Research UK, 2021).

Paediatric ALL typically follows a more favourable clinical course compared to adults, with most patients achieving remission. Advances in treatment regimen and diagnostic technologies have contributed to the substantial improvement in rates of remission and survival. Five-year survival rates for children exceed 90% in many cases (Malard and Mohty, 2020), although long-term survival rates in adults are lower, ranging from 30% to 40% (Pulte et al., 2014). In this analysis, we employ paediatric and young adult ALL as the reference case due to the availability of robust long-term survival data and real-world evidence in this population.

Health-related quality of life (HRQoL) studies in ALL highlight consistent patterns of impairment during treatment, and variable recovery post-therapy. Survivorship studies demonstrate that overall HRQoL for ALL patients post-treatment completion was either similar to or higher than patients on active treatment, albeit patients still reported lower physical and psychosocial functioning compared to population norms or siblings (Garas et al., 2019). The majority of long-term survivors of paediatric cancer are likely to experience at least one late effect during survivorship, including fatigue, neurological conditions, pain, and neurocognitive difficulties (Vetsch et al., 2018). A prospective, cross-sectional study of childhood ALL survivors found that neurological symptoms were present in 83% of survivors, and high doses of intrathecal chemotherapy and relapse predisposed survivors to impaired QoL (Khan et al., 2014).

Survivors of ALL treated with conventional chemotherapy face substantial long-term health impacts. Neurocognitive impairments, including deficits in attention, memory, and executive function, are common, and these can adversely affect academic attainment and long-term employment prospects (Iyer et al., 2015). In addition, chronic health conditions such as endocrine complications (e.g., growth hormone deficiencies, hypothyroidism), cardiometabolic conditions, and fatigue are frequent among survivors exposed to intensive therapies such as stem cell transplants (Shalitin et al., 2018; Chow et al., 2010; Kelkar, Antin and Shapiro, 2023). These conditions can significantly impair long-term workforce participation, especially among individuals with lower educational attainment. By comparison, CAR T-cell therapy—while associated with acute toxicities like cytokine

release syndrome (CRS) and neurotoxicity—has demonstrated more favourable long-term recovery patterns. HRQoL often rebounds within six months post-treatment, often reaching levels comparable to or better than those observed in patients receiving conventional care (Johnson et al., 2023).

The long-term socioeconomic burden of ALL also extends to caregivers. Caregiver responsibilities can lead to reduced working hours, missed workdays, and decreased efficiency while at work, resulting in measurable productivity losses that contribute to the broader socioeconomic impact of the disease. In families of children with advanced paediatric cancer, up to 94% of parents experienced some form of work disruption, including reduced hours, missed workdays, or leaving employment altogether (Bona et al., 2014). One study reported that parents missed an average of 17.3 workdays within the first month following their child's diagnosis (Fluchel et al., 2014). While CAR-T therapy may shorten the duration of active treatment as well as reduce the frequency of long-term hospital visits compared to multi-phase chemotherapy regimens, it is expected that caregiving needs remain elevated well into survivorship. Families will still need to navigate follow-up care, late effect surveillance, and psychosocial support needs, often without the same level of clinical oversight provided during initial treatment.

Standard treatment for ALL typically involves multi-phase chemotherapy combined with central nervous system (CNS) prophylaxis. Induction therapy aims to achieve remission, followed by consolidation and maintenance phases lasting up to three years. Intrathecal chemotherapy is often employed to prevent CNS relapse, given the limited penetration of systemic drugs into this area. While effective in achieving high remission rates, particularly in children, standard chemotherapy is associated with substantial toxicities such as myelosuppression, neurocognitive impairment, and increased infection risk. Stem cell transplantation may be considered for high-risk or relapsed cases.

Modern treatments for ALL have been revolutionised by the introduction of CAR T-cell therapy, particularly for relapsed or refractory B-cell ALL. CAR-T therapy, such as tisagenlecleucel, targets CD19-positive leukaemia cells with precision, achieving durable remissions in patients who fail standard therapies. Unlike chemotherapy, CAR-T therapy minimises off-target effects but carries unique risks like cytokine release syndrome (CRS) and neurotoxicity. Studies show that CAR-T-treated patients experience faster recovery in terms of health-related quality of life (HRQoL) compared to those undergoing traditional treatments. Additionally, targeted therapies like tyrosine kinase inhibitors (e.g., imatinib) are increasingly used in Philadelphia chromosome-positive ALL cases, further improving outcomes. These advancements highlight a shift towards personalised and less toxic therapeutic approaches in ALL management.

Methods

For this case study, we develop a state-transition model to evaluate the costs and benefits of CGT compared to standard of care for paediatric and young adult patients with relapsed or refractory B-cell ALL. CAR-T therapies are actively used in clinical practice in this population and are therefore modelled as the CGT intervention. The model considers disease progression, treatment response, resource use, and patient outcomes. Our approach is structured to align with recent economic evaluations of CAR-T therapies for B-cell ALL, to ensure it is reflective of current care practices.

Scenarios

We consider two scenarios for this case study. ALL provides a well-established evidence base for the effectiveness of CAR-T treatments, having been in clinical practice for close to a decade. Given this, we focus the difference between the scenarios on any

uncertainties in parameters that are impacted by real-world evidence and those that are heavily informed by assumptions.

Table 17 outlines key differences with scenario A and B. Scenario A considers a more credible scenario, with parameters and assumptions derived from clinical trials, published HTA appraisals and economic models published in the literature. Scenario B explores plausible optimistic estimates and assumptions largely based on benefits to the economy that arise from health improvements associated with CGT, such as improved socioeconomic outcomes and reduced caregiver burden.

We explore parameters related to intravenous immunoglobulin treatment, which is commonly used in conjunction with CAR-T therapy to manage hypogammaglobulinaemia, a frequent side-effect that results from the depletion of normal B cells. These parameters were highlighted as highly uncertain in the NICE appraisal for tisagenlecleucel for CAR-T therapy. Scenario A adopts a conservative approach, where IVIG use is informed by a real-world evidence dataset (the Systemic Anti-Cancer Therapy [SACT] dataset) and assumes greater hospital admissions and duration of use associated with CGT treatment. Scenario B aligns with clinical trial data.

The burden of care for children with cancer often falls to families, particularly parents, whose work productivity is affected by the need to attend frequent hospital appointments, manage complex treatment schedules, and provide ongoing care at home. Scenario A assumes equivalent caregiving requirements across treatment arms, reflecting a conservative base case. We assume high caregiving intensity during 'Initial Treatment; estimates for this state is informed by Fluchel et al. (2014), which reports 17.3 missed workdays among parents of children with cancer in the first month post-diagnosis. We also assume 'Relapse' and 'Remission after transplant' health states to have increased caregiving demands relative to the 'Remission' health state based on clinical opinion and previous appraisals. For these states, we apply productivity loss estimates from Angioli et al. (2015), a broader study on caregiving in cancer given limited treatment-specific data. The study found that employed caregivers reported an average of 8.7% work time lost due to absenteeism and a 12.8% reduction in productivity from presenteeism, with an overall carer productivity loss of 20.67% (Angioli et al., 2015). For caregivers of patients undergoing relapse after transplant, we model additional assumptions based on evidence showing caregivers miss approximately 25 work days in the year following transplant (Biddell et al., 2022) In both treatment arms, the 'Remission' and 'Cure' health states is assumed to have no ongoing caregiver burden.

Scenario B incorporates differential caregiver burden by treatment and disease severity. We assume high caregiving intensity to extend into the relapse health state for SoC patients, given that these patients are often still treated with additional rounds of therapy or other high-dose salvage regimens. We would expect high caregiver burden given the need for ongoing hospital visits for treatment and management of any adverse effects. Based on this, we apply Fluchel et al.'s (2014) estimate of 17.3 missed workdays during both the initial treatment and relapse health states for the standard chemotherapy arm.

In contrast, CAR-T therapy is modelled as requiring intensive caregiving only during the initial treatment health state, reflecting the need for close monitoring of cytokine release syndrome and neurotoxicity, but with reduced long-term burden due to its single administration and shorter treatment trajectory. For relapse states following CAR-T, we apply the broader productivity loss estimates from Angioli et al. (2015): 8.7% absenteeism and 12.8% presenteeism. All other inputs are aligned with scenario A, including parameters for transplant and cure health states.

Socioeconomic parameters were considered for inclusion as part of scenario B in this analysis, given the growing evidence of long-term functional and societal impacts of ALL treatment on a paediatric and adult population (Mody et al., 2008). These parameters can help capture the full spectrum of long-term impacts on survivors and society. Survivors of

treatment, particularly treatment that is considered curative early in life, often face challenges that extend beyond immediate health concerns, and affect their educational achievements and future work productivity. We conceptualised the level of socioeconomic participation in two ways:

(1) school absences, where patients and survivors of treatment are found to have high absenteeism relative to the general population (French et al., 2013);

(2) cognitive impairments resulting from treatment, particularly cranial irradiation and high-dose chemotherapy which affect memory, attention, and executive function, which can persist into adulthood (Iyer et al., 2015).

Educational and cognitive challenges are likely to translate into direct economic consequences; increased school absences and cognitive impairments are linked to reduced educational attainment and future employment challenges (Krull et al., 2013; Dräger, Klein and Sosu, 2024). A US study estimates that adult survivors of childhood cancer experience an excess annual productivity loss of $5,086 per person, highlighting the lasting effects of a childhood cancer diagnosis (Guy et al., 2016).

Emerging therapies, such as CAR-T cell therapy, may offer different long-term socioeconomic outcomes compared to existing treatments. While CAR-T therapy involves intensive short-term care, its potential for sustained remission could reduce long-term cognitive and educational disruptions. Nevertheless, more comprehensive longitudinal studies are needed to fully understand these differences.

Table 17 Acute lymphoblastic leukaemia scenarios

PARAMETER	SCENARIO A	SOURCE / EXPLANATION A	SCENARIO B	SOURCE / EXPLANATION B
PROPORTION OF PATIENTS WITH / DURATION OF INTRAVENOUS IMMUNOGLOBULIN (IVIG) TREATMENT	47% / 18 months	In line with NICE evaluation of tisagenlecleucel (NICE, 2024c), parameters related to IVIG treatment were informed by a real-world evidence dataset, the Systemic Anti-Cancer Therapy (SACT) dataset	30.4% / 11.4 months	ELIANA trial
CAREGIVING PARAMETERS	**Initial treatment:** 17.3 missed workdays in the month following infusion **Relapse:** Carer productivity loss (20.67%) **Transplant:** 25 missed workdays for the year following transplant **Cure:** No caregiving burden assumed	These values are applied to the proportion of the population that is economically active, as per ONS data. Sources for initial treatment, remission / relapse and transplant states are respectively Fluchel et al. (2014), Angioli et al. (2015) and Biddell et al. (2022)	**Relapse:** Assumed 17.3 missed workdays in the month, to align with high caregiving intensity needs in relapse	

Despite the importance of these factors, modelling educational and other longer term socioeconomic outcomes remains challenging due to a lack of robust data. These impacts typically manifest over extended time periods and are unlikely to yield measurable economic consequences within the short- to medium-term time horizon of this analysis. Additionally, there is limited evidence on how different types of treatment influence the level of socioeconomic burden, further constraining the inclusion of these outcomes in the model.

Given this, we did not model these parameters in scenario B of the analysis. There is a need for further research into developing methodologies to integrate longer-term productivity losses or gains and human capital impacts into economic evaluations. This is important to ensure a more comprehensive assessment of treatment value.

Population

The population we model is paediatric and young adult patients (under the age of 25 years) with relapsed (either after a transplant or after two or more lines of treatment) or refractory (r/r) B-cell ALL. We model this population because CAR-T therapies are actively used in clinical practice for treating r/r B-ALL in these age groups.

The mean age is modelled to be 12 years, with 43.04% of the population female. This is in line with a NICE appraisal for a CAR-T therapy for ALL in the selected population (NICE, 2024c).

In the UK, there were 765 new cases of ALL diagnosed in the UK each year from 2017 to 2019, with 484 cases (63.3%) were in patients aged 0 to 24 years (Cancer Research UK, 2021). Clinical evidence suggests that approximately 15% to 20% of patients have been reported to experience relapsed disease within the first two years of achieving complete remission from first-line chemotherapy (Pui et al., 2015). Given this, we have conservatively modelled an incident relapsed/refractory population of 38 patients. Of these 38 patients, we assume 81.4% patients are eligible for CAR-T therapy, based on the CAR-T population identified in the NICE appraisal of tisagenlecleucel which restricts the eligible patient population based on any adverse events or failures in the manufacturing process, giving us an eligible population of 31 patients.

Intervention

We model the intervention as a CAR-T therapy, using effectiveness data related to tisagenlecleucel, which is currently the only CAR-T therapy licensed for use in paediatric and young adult patients with relapsed or refractory B-cell ALL in the UK. It is an established and effective treatment option in this population. Tisagenlecleucel has demonstrated high efficacy in clinical trials and real-world studies; the ELIANA trial reported an 81% complete remission (CR) rate in pediatric and young adult patients with R/R B-cell ALL, with a 12-month overall survival (OS) rate of 76% and durable remissions in responders (Maude et al., 2018).

The intervention is delivered as a single, one-time dose of a CGT. We further include the costs associated with pre-treatment procedures (leukapheresis to collect T cells), lymphodepleting chemotherapy to enhance CAR-T efficacy and bridging chemotherapy to stabilize disease while CAR-T cells are manufactured.

Comparator

The standard of care (SoC) for paediatric and young adult patients (up to 25 years) with relapsed or refractory (r/r) B-cell ALL in the UK includes a mix of immunotherapies and salvage chemotherapy regimens. In line with the NICE appraisal of tisagenlecleucel (TA975), the relevant comparators for this population include blinatumomab and salvage chemotherapy; in this analysis, we consider a SoC as a basket comparator of these two

treatments forming a basket of comparators representing routine NHS practice (NICE, 2024c).

Blinatumomab, a bispecific T-cell engager targeting CD19, is frequently used in paediatric patients with primary refractory disease or those in second or subsequent relapse. The treatment is administered as a continuous intravenous infusion over 28 days per cycle, typically delivered via a central venous catheter in an inpatient or ambulatory setting. Each cycle is followed by a 14-day treatment-free interval, and patients may receive up to five cycles depending on response and tolerance. Clinical trial evidence demonstrates improved complete remission (CR) rates and overall survival compared to conventional chemotherapy, with fewer grade 3/4 adverse events (Brown et al., 2021a; von Stackelberg et al., 2016).

Salvage chemotherapy, typically consisting of intensive multi-agent regimens such as FLAG-IDA, continues to be widely used for patients who are ineligible for, or have previously failed, immunotherapy. The FLAG-IDA regimen includes fludarabine, cytarabine (Ara-C), granulocyte-colony stimulating factor (G-CSF), and idarubicin, typically delivered over 4—5 days in repeated cycles. These regimens are associated with significant toxicity, requiring inpatient admission, intensive supportive care, and prophylactic antimicrobials. Nevertheless, they remain a mainstay in clinical practice, especially when aiming to induce remission prior to allogeneic stem cell transplant (allo-SCT), or in settings where access to immunotherapies is limited.

We do not include inotuzumab ozogamicin, a CD22-targeted antibody—drug conjugate also licensed for use in r/r B-cell ALL, within the basket of comparators. While inotuzumab ozogamicin may be offered to select patients, particularly in older adolescents and young adults with confirmed CD22 expression, its routine use in younger paediatric patients is more limited. The use of inotuzumab in this population is often restricted to compassionate use or managed access schemes, making it difficult to capture within standard pathways of care. Additionally, there is limited clinical trial evidence evaluating the efficacy and long-term outcomes of inotuzumab specifically in paediatric patients.

Allogeneic stem cell transplantation is not considered a comparator in this model. It is instead incorporated within the model structure, wherein patients can transition into hematopoietic stem cell transplantation (HSCT) health states after either relapse or remission. This is primarily to account for the fact that blinatumomab and clofarabine-containing therapies are generally seen as bridges to transplantation in clinical practice, wherein they are considered insufficient to ensure durable long-term remission in relapsed disease.

Outcomes

Outcomes focus on both achieving and maintaining complete remission (CR), with patients considered “functionally cured” of ALL. Reaching CR is associated with improved health-related quality of life, longer survival, fewer chemotherapy-related adverse events, and reduced use of healthcare resources. Patients in remission are also expected to achieve better educational outcomes, have improved future workplace productivity, and place a reduced burden on caregivers.

Key outcome measures include life years gained, QALYs, total healthcare costs, and productivity losses; these reflect the impact on both patients and their caregivers. Educational outcomes are likely to improve with sustained remission, and we sought to identify relevant parameters to inform the estimation of education-related outcomes at the individual and system-level. However, we were unable to identify relevant evidence and these outcomes are therefore excluded from the current analysis.

Model structure

Figure 2 demonstrates the model structure for this analysis, which is a seven-state cohort transition model, with a monthly cycle length. The structure is adapted from an existing cohort model published for paediatric and young adult patients with relapsed or refractory B-cell ALL (Lin et al., 2018).

Initial treatment: Patients enter the model in this state, receiving either CAR-T therapy or SoC treatment, such as blinatumomab or salvage chemotherapy. Patients who achieve remission transition to the Remission state. Patients who do not achieve remission either transition to Relapse or refractory state if their disease progresses or to death.

Remission: In this state, patients are monitored for disease recurrence. A subset of these patients may undergo allogeneic stem cell transplantation (allo-SCT) as part of consolidation therapy. Patients may remain in remission, relapse, transition to the cure state if they remain relapse-free for a pre-specified period, or transition to death.

Relapse or refractory: Patients who do not achieve or who lose remission transition to this state. They may receive allo-SCT if eligible. Death is the only possible transition from this state.

Remission after transplant: Patients who achieve a second remission after transplant may remain in this state, relapse, transition to the cure state if they remain relapse-free for a pre-specified period, or transition to death.

Relapse after transplant: Patients whose disease returns after allo-SCT move into this state. These patients are typically offered palliative treatment and may remain in this state or transition to death.

Cure: This state represents patients who remain in remission (either pre- or post-transplant) for five years and are considered functionally cured. Patients in this state can only transition to death. These patients are assumed to experience a higher background mortality than a person of similar age from the general population, based on existing evidence from relevant populations.

Death: This is an absorbing state (no transition out of this state). A one-off terminal care cost is applied in this state.

Table 18 sets out the transition probabilities for the model.

Table 18 Transition probabilities for acute lymphoblastic leukaemia

STANDARD OF CARE	State	To: Initial tx	Remission	Relapse	Remission after SCT	Relapse after SCT	Cure	Death
From	**Initial tx**	0.00	0.79	0.18	0.00	0.00	0.00	0.03
	Remission	0.00	0.95	0.02	0.02	0.00	0.00	0.01
	Relapse	0.00	0.00	0.76	0.00	0.00	0.00	0.24
	Remission after SCT	0.00	0.00	0.00	0.98	0.01	0.00	0.01
	Relapse after SCT	0.00	0.00	0.00	0.00	0.94	0.00	0.06
	Cure	0.00	0.00	0.00	0.00	0.00	0.97	0.03
	Death	0.00	0.00	0.00	0.00	0.00	0.00	1.00

CELL AND GENE THERAPY	State	To: Initial tx	Remission	Relapse	Remission after SCT	Relapse after SCT	Cure	Death
From	**Initial tx**	0.00	0.94	0.06	0.00	0.00	0.00	0.00
	Remission	0.00	0.95	0.02	0.00	0.00	0.01	0.02
	Relapse	0.00	0.00	0.89	0.00	0.00	0.00	0.11
	Remission after SCT	0.00	0.00	0.00	0.97	0.01	0.01	0.01
	Relapse after SCT	0.00	0.00	0.00	0.00	0.94	0.00	0.06
	Cure	0.00	0.00	0.00	0.00	0.00	0.98	0.02
	Death	0.00	0.00	0.00	0.00	0.00	0.00	1.00

Notes: The values indicated in red are non-zero but have been rounded for consistency.
Abbreviations: SCT: stem-cell transplantation.

This analysis sources key clinical inputs for the intervention, including remission rates, overall survival, relapse-free survival, and adverse events—from the pivotal phase II ELIANA trial for tisagenlecleucel and supporting real-world data where applicable.

Inputs specific to the CGT arm are aligned with those used in the NICE technology appraisal TA975, which informed the recommendation of tisagenlecleucel for paediatric and young adult patients with relapsed or refractory B-cell ALL (NICE, 2024c). Comparator arm inputs are derived from published clinical trials, including AALL1331, and supplemented with data from prior economic evaluations of immunotherapy in paediatric ALL (Hogan et al., 2023; von Stackelberg et al., 2016; Brown et al., 2021a; Jeha et al., 2006).

Simplifying assumptions

This analysis includes several simplifying assumptions, compared to economic evaluations and appraisals of the same therapy. This was done to enable consistency with NICE appraisals and prior evaluations of CAR-T therapy in ALL, and to allow for broader generalisability and comparison with other case studies.

Defining the population

In this analysis, we model a cohort of 'initial' patients entering the relapsed or refractory (r/r) B-cell ALL setting, rather than including a broader population that spans multiple lines of prior treatment. Patients are assumed to enter the model at the point of first relapse or primary refractory disease, consistent with eligibility criteria used in clinical trials for CAR-T and other r/r therapies. Modelling at this consistent entry point ensures alignment with available trial data and avoids heterogeneity related to multiple prior treatment lines or disease outcomes.

Additionally, we do not model a prevalent population, as patients with r/r ALL are generally treated immediately upon relapse or refractory progression and do not remain in a stable "prevalent" state. Unlike chronic conditions, there is no clinically meaningful period where a prevalent, untreated r/r population would accumulate.

Eligibility for HSCT

We conservatively assume that only patients who achieve complete remission (CR) are eligible to proceed to haematopoietic stem cell transplantation (HSCT). In clinical practice, HSCT is typically considered in patients in second complete remission (CR2) or those with high-risk features in CR1, particularly in relapsed or refractory B-cell ALL (Brown et al., 2021b). Performing HSCT in active disease (i.e., without prior remission) is associated with poor outcomes and is rarely undertaken in paediatric patients due to high transplant-related mortality and low curative potential (Okamoto et al., 2020). This assumption aligns with published treatment guidelines, simplifies the model structure by restricting HSCT transitions to post-remission states only and avoids overestimating the benefits of HSCT in populations where it is not routinely used.

Cure assumptions

We assume a fixed percentage of patients are cured by each treatment, consistent with assumptions used in the NICE TA975 appraisal and related economic models (Lin et al., 2018; NICE, 2024c). In the model, "cure" is defined as sustained long-term remission without the need for further treatment or risk of relapse. The assumed cure rates are: 1) CAR-T therapy: 40%; 2) Blinatumomab: 25%; 3) Salvage chemotherapy: 10%. These values are derived from expert opinion and extrapolated survival curves from the NICE TA975 appraisal based on data from key trials (NICE, 2024c; Maude et al., 2018; Hogan et al., 2023). Using fixed cure rates helps avoid the need for complex long-term survival modelling, which is difficult when follow-up data are limited.

Parameter values for ALL

Table 19 Parameter values for acute lymphoblastic leukaemia

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
EPIDEMIOLOGY	Mean age at baseline (years)	12	ELIANA trial, based on TA975
	Proportion of female	43.04%	ELIANA trial, based on TA975
	Incident ALL population	484	Cancer Research UK, 2017—2019
	Relapsed/refractory population eligible for CAR-T	31	Based on the assumption that roughly 15 per 100 patients relapse over 2 years and only 81.4% of patients are eligible for CAR-T infusion, based on TA975

PATIENT UTILITIES	Patient utility — Initial treatment	0.78	Lin et al. (2018b)
	Patient utility — Remission	0.88	Lin et al. (2018b)
	Patient utility — Relapse	0.76	Lin et al. (2018b)
	Patient utility — Remission after transplant	0.8	Lin et al. (2018b)
	Patient utility — Relapse after transplant	0.73	Lin et al. (2018b)
	Patient utility — Cure	0.86	Lin et al. (2018b)
	Patient utility — Death	0	Lin et al. (2018b)
HEALTH-STATE COSTS FOR CGT[1]	Treatment costs (excluding CAR-T infusion)	£47,698.57	Derived from TA975
	Healthcare costs — Remission	£640.50	Derived from TA975
	Healthcare costs — Relapse	£209.17	Derived from TA975
	Healthcare costs — Remission after transplant	£122.51	Derived from TA975
	Healthcare costs — Relapse after transplant	£288.02	Derived from TA975
	Healthcare costs — Cure	£30.08	Derived from TA975
	Healthcare costs — Death	£0.00	Derived from TA975
HEALTH-STATE COSTS FOR SOC[1]	Treatment costs	£57,349.40	Derived from TA975
	Healthcare costs — Remission	£409.42	Derived from TA975
	Healthcare costs — Relapse	£288.02	Derived from TA975
	Healthcare costs — Remission after transplant	£121.41	Derived from TA975
	Healthcare costs — Relapse after transplant	£288.02	Derived from TA975
	Healthcare costs — Cure	£30.08	Derived from TA975
	Healthcare costs — Death	£0.00	Derived from TA975
ONE-OFF COSTS AND DISUTILITIES[1]	Costs — HSCT	£165,613.15	Derived from TA975
	Costs — HSCT, follow-up	£47,906.88	Derived from TA975
	Disutilities — HSCT	0.04	Derived from Sung et al. (2003), adjusted for the cycle
EVENT PROBABILITIES	Probability — CRS (CGT)	48.10%	Derived from TA975
	Probability — CRS (SoC)	2.86%	This is based on the assumption that 50% of the SoC arm is treated with blinatumomab, with a CRS rate of 5.71% based on von Stackelberg et al. (2016)
	Probability — B-cell aplasia (CGT only; Scenario A)	47.00%	NICE SACT dataset
	Probability — B-cell aplasia (CGT only; Scenario B)	30.40%	Derived from TA975
ADVERSE EVENTS[1]	Costs — CRS	£38,485.61	Derived from TA975
	Costs — B-cell aplasia (CGT only; Scenario A)	£35,138.9	Based on NICE SACT dataset, where treatment for B-cell aplasia is expected to be 18 months

	Costs — B-cell aplasia (CGT only; Scenario B)	£22,254.64	Based on TA975, where treatment for B-cell aplasia is expected to be 11.4 months
	Disutilities — CRS	0.03	Derived from TA975
	Disutilities — B-cell aplasia	0.00	
DEATH COST[1]	End-of-life care	£11,989.12	NHS Reference Costs 2023/2024, weighted average of Non-Elective Long Stay Paediatric Acute Lymphoblastic Leukaemia codes

1. All costs are inflated to and reported in 2024 GBP

Table 20 Productivity effects for acute lymphoblastic leukaemia

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
GENERAL POPULATION INPUTS	Retirement age	68	(NICE, 2024)
	Days of work, per year	253.25	Calculated
	Hours of work, per day	6.36	Average working hours per week (ONS, 2024a)
	Value of working time: lost production	£18.93	Average hourly wage (ONS, 2024a)
	Proportion of the population economically inactive	21.80%	ONS (2024a)
	Value of working time: lost production	£37,430	Median salary UK (ONS, 2024c)
CARER PRODUCTIVITY LOSS	Carer work productivity loss, %	20.67%	(Angioli et al., 2015)
	Missed workdays post-diagnosis, monthly	17.3	(Fluchel et al., 2014)
	Missed workdays post-transplant, monthly	2.08	(Biddell et al., 2022)
	Proportion of caregivers experiencing work disruption (Scenario B only)	94.00%	(Bona et al., 2014)

Steady-state results for ALL

Table 21 Steady-state (annual) results, ALL, scenario A

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£3,389,283,698	£3,054,067,365	£335,216,333
	Systems	-£175,266,600	-£724,573,612	£549,307,012
	National economy	-£2,127,202,019	-£2,120,976,085	-£6,225,934

HEALTH OUTCOMES	QALYs	48,418	43,630	4,789 QALYs
	Life years	61,605	61,344	261 LYs

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Table 22 Steady-state (annual) results, ALL, scenario B

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£4,172,813,158	£3,751,925,510	£420,887,647
	Systems	-£168,062,024	-£890,139,573	£722,077,549
	National economy	-£2,615,131,940	-£2,605,621,726	-£9,510,214
HEALTH OUTCOMES	QALYs	59,612	53,599	6,013 QALYs
	Life years	75,760	75,362	398 LYs

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Comparison of results to similar evaluations

In our analysis, we consider a CAR-T therapy as the CGT intended to alter disease progression in ALL. Currently, tisagenlecleucel (Kymriah) is the only licensed CAR-T option for children and young adults with relapsed or refractory B-cell ALL. The therapy modelled here is modelled after tisagenlecleucel and uses both published clinical and cost parameters related to the treatment.

We alter our original analysis by simulating outcomes for one prevalent patient over a lifetime horizon to enable meaningful comparison with existing evaluations of tisagenlecleucel in ALL. To maintain consistency in methodology, we also incorporated costs of CAR-T treatment into our model, reflecting approaches taken in prior analyses.

For reference, we selected three comparator studies: 1) (NICE, 2024c), the NICE technology appraisal of tisagenlecleucel, which examines cost-effectiveness within the NHS, 2) (Lin et al., 2018b), a published economic evaluation of tisagenlecleucel in the United States, and 3) (Sarkar et al., 2019), which employs a microsimulation model to estimate long-term outcomes and value of tisagenlecleucel using trial data inputs.

Per-patient discounted outcomes for scenarios A and B are presented in Table 23, alongside findings from the two selected studies. We do not include a cost comparison for any of the studies. Although the NICE technology appraisal of tisagenlecleucel was conducted within a comparable UK setting, the incremental costs and QALYs are redacted, limiting meaningful comparison. The evaluations by Lin et al. (2018) and Sarkar et al. (2019) both employ resource use and cost inputs based on the US healthcare system, which differs in pricing structures and clinical practice patterns, reducing the transferability of cost outcomes to a UK-specific context.

The QALY and life year outcomes in our analysis do not fully align with those reported in the comparator studies, and several factors may explain this divergence. Notably, our model adopts a shorter effective time horizon than selected comparator studies (which all employ a lifetime horizon). This is likely to truncate the long-term survival benefits associated with CAR-T therapy, and particularly affects life year gains, as curative effects and survival plateaus often emerge well beyond the initial follow-up period. We adopt a more conservative survival assumptions, borrowing reported transitions and response rates from relevant literature where possible. This may underestimate time spent in high-utility health states or the curative potential of CAR-T therapy, particularly in younger

patients. Regardless, the selected studies all report substantial improvements in health benefit associated with CAR-T therapies. While of lower magnitude, our analysis still demonstrates a measurable clinical benefit, suggesting that the macroeconomic value of CGT in this case may be underestimated.

Table 23 Tisagenlecleucel evaluation comparison

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS (3.5% FOR NICE; 3% OTHERWISE)	INCREMENTAL GAIN DISCOUNTED LYS (3.5% FOR NICE; 3% OTHERWISE)
NICE TA975	UK	Tisagenlecleucel vs blinatumomab vs salvage chemotherapy	NA	vs blinatumomab, 7.13 vs salvage chemotherapy, 8.18
Lin et al., 2018	US	Tisagenlecleucel (40% cure assumption) vs blinatumomab vs clofarabine combination vs clofarabine monotherapy	vs blinatumomab, 5.17 vs blinatumomab, 5.62	vs blinatumomab, 12.05 vs clofarabine combination, 12.05 vs clofarabine monotherapy, 13
Sarkar et al., 2019	US	Tisagenlecleucel vs standard therapy	8.18	NA
Current analysis (Scenario A-Scenario B)	UK	CGT versus SoC	4.46 / 5.18	4.75 / 5.57

C. Acute myeloid leukaemia case study details

Acute myeloid leukaemia (AML) is a rapidly progressing haematological malignancy characterised by the abnormal proliferation of immature myeloid cells (Juliusson, Lehmann and Lazarevic, 2021). It is the most prevalent form of acute leukaemia in adults, with a higher incidence observed in individuals over 60 years of age (Vakiti, Reynolds and Mewawalla, 2024).

AML arises from the clonal expansion of myeloid precursors in the bone marrow, resulting in ineffective erythropoiesis and megakaryopoiesis, rapid bone marrow failure, and insufficient production of red blood cells and platelets. The disease is defined by the accumulation of immature myeloblasts in bone marrow and peripheral blood, impaired production of normal blood cells, and potential infiltration of other organs such as the liver, spleen, and lymph nodes (Vakiti, Reynolds and Mewawalla, 2024).

The clinical course of AML is characterised by rapid progression, necessitating prompt initiation of treatment upon diagnosis. Without intervention, AML can lead to mortality within months of diagnosis (National organisation for rare disorders, 2024). Even with current treatment modalities, prognosis remains suboptimal, particularly in older patient populations.

In the UK, AML accounts for around 2,945 new cases each year (Cancer Research UK, 2019). The disease demonstrates a higher prevalence in adults over 60 years old. Five-year survival rates of patients in the UK exhibit significant age-related disparities, with patients under 60 years showing a survival rate of over 35%, while those over 60 years have a survival rate below 15% or less (Haematological Malignancy Research Network (HMRN), 2024).

The disease and its treatments can substantially affect patients' health-related quality of life (HRQoL). A systematic review of HRQoL in AML patients found that HRQoL declined quickly after diagnosis and treatment initiation, with physical symptoms such as fatigue, pain, and dyspnoea commonly reported (Korol et al., 2017). Fatigue was identified as the most problematic symptom domain in patients, irrespective of their treatment status (Bryant et al., 2015). Psychological distress, such as anxiety and depression, is often reported amongst patients treated with 'intensive' chemotherapy requiring prolonged hospitalisations (El-Jawahri et al., 2019; Lockwood et al., 2020). Impact on social wellbeing is also a notable concern, with one study estimating up to 69% of AML patients having experienced at least one form of social toxicity, such as changes in work, school or home life (Fortune et al., 2023).

A study on work absenteeism and disability among AML patients and their caregivers reported significant impacts on workplace absence and disability days. In the year following an AML diagnosis, patients experienced a significant increase in short-term disability (STD) and long-term disability (LTD) leave days, with claims rising sixfold and fourfold, respectively. Caregivers' workplace absence peaked in the first two months post-diagnosis and remained elevated thereafter (Pandya et al., 2024).

Standard treatment for AML typically involves intensive chemotherapy, and in selected cases, chemotherapy combined with HSCT (Kantarjian et al., 2021). Treatment initiation is time-sensitive due to the aggressive nature of the disease. Despite advancements in treatment protocols, AML continues to present significant therapeutic challenges, particularly in older patient populations.

Recent advances in molecular characterisation have led to improved risk stratification and the development of targeted therapies. The European LeukemiaNET (ELN) 2022 guidelines emphasise molecular characterisation and risk stratification for individuals with AML, providing updated data on these aspects (Döhner et al., 2022). These

advancements have resulted in the approval of several new treatments in recent years, potentially offering improved outcomes in the future.

Methods

In this case study, we developed a state-transition model to evaluate the costs and benefits of CGT compared to standard of care for patients with untreated AML. We model the CGT as CAR-T therapy, given that CAR-T therapies are currently in development for AML and are used to treat related cancers. The model accounts for disease progression, treatment response, healthcare resource utilisation, and patient outcomes. Our analysis incorporates current clinical evidence where available and uses evidence-based assumptions otherwise. We structured our approach to align with previous economic appraisals conducted for AML therapies, to ensure comparability with existing evaluations.

Scenarios

As outlined above, we consider two separate scenarios for this case study to account for uncertainties in treatment effectiveness, given the treatment is still in the pipeline. Table 24 below outlines the differences between the scenarios.

Scenario A considers a more credible scenario, where parameters and assumptions are derived from clinical trials or in line with current use in similar indications, such as ALL (where CAR-T therapy use is already approved and in use). The population receiving CAR-T therapy is based on the CAR-T population identified in the NICE appraisal of tisagenlecleucel, wherein the eligible proportion of patients for CAR-T therapy is estimated based on any adverse events or failures in the manufacturing process. (NICE, 2024c). In terms of CGT therapy effectiveness, the probability of resistant disease amongst patients is informed by empirical estimates associated with current antibody-based therapy for AML (Russell-Smith et al., 2021). A proportion of CAR-T patients are assumed to receive HSCT after relapse in line with estimates for current antibody-based therapy for AML (Russell-Smith et al., 2021), given that HSCT is currently an available option for AML patients subject to donor availability and literature suggesting there may overlap between CAR-T treatment and HSCT (Goldsmith et al., 2022).

Scenario B presents a more optimistic scenario and employs assumptions allowing for higher and more sustained treatment effectiveness. Here, all untreated AML patients within the assessed population will be eligible for CAR-T treatment. Scenario B assumes lower probabilities of resistant disease amongst CAR-T patients, based on evidence in the literature that CAR-T therapies are associated with higher rates of complete remission compared SoC (Cappell and Kochenderfer, 2023).

It is assumed that CAR-T patients do not undergo HSCT treatment, aligning with current evidence that CAR-T therapy provides durable remissions without the need for subsequent transplantation (Cappell and Kochenderfer, 2023).

Table 24 Acute myeloid leukaemia scenarios

PARAMETER	SCENARIO A	SOURCE / EXPLANATION A	SCENARIO B	SOURCE / EXPLANATION B
Proportion of incident population eligible for CAR-T therapy	81.40%	In line with NICE evaluation of tisagenlecleucel (NICE, 2024c), the proportion of leukaemia patients eligible for CAR-T therapy is restricted based on adverse events or failures in the manufacturing process	100.00%	The entire untreated AML population is assumed eligible for CAR-T therapy
Probability of resistant disease after receiving induction treatment	12.00%	Assumed equal to probability of resistant disease derived for gemtuzumab ozogamicin patients in ALFA-0701 (Russell-Smith et al., 2021)	10.00%	Assumption
HSCT utilisation for relapse AML patients	9.58%	Assumed equal to rate of HSCT use for gemtuzumab ozogamicin patients in ALFA-0701 (Russell-Smith et al., 2021)	0.00%	Assumption

Population

The population we modelled was adult patients with untreated AML. We model the mean age to be 61.2 years, with 50.93% of the population female. This is in line with similar NICE appraisals of therapies for untreated AML (Russell-Smith et al., 2021).

For this analysis, we focus exclusively on an incident population of AML — assuming that there is no untreated prevalent population — as this approach aligns with the typical progression and treatment patterns associated with the disease. Given the high mortality rate and the need for timely treatment, it is standard to consider only newly diagnosed patients. This restriction also allows us to limit the analysis to untreated AML patients, avoiding the inclusion of those with prior relapses, who follow distinct treatment pathways and may introduce confounding factors.

In the UK, it has been estimated that approximately 2,945 new cases of AML are diagnosed each year in individuals aged 18 years and older (Cancer Research UK, 2019). In Scenario A, we assume that 81.4% of patients are eligible for CGT, while the remaining patients are considered ineligible due to adverse events or failures in the manufacturing process (NICE, 2024c). This results in a starting population, as well as subsequent incident population, of 2397 patients per year. Scenario B assumes all patients are eligible for CGT, resulting in a starting and incident population of 2,945 patients per year.

Intervention

We assume that patients have access to one or more hypothetical CAR-T therapies. The success of CAR-T based therapies in cancer, including other types of leukaemias and lymphomas, has led to efforts to develop immune-based approaches for AML treatment, encompassing both antibody-based therapies and cellular strategies. Currently, there are several ongoing trials exploring the use of CAR-T cells, including both autologous and allogeneic CAR-T cells targeting markers such as CD123, CD33, and CLL1 for patients with acute myeloid leukaemia (Koneru et al., 2022; Shah et al., 2023).

The intervention involves a one-off single dose of a CGT, along with the costs of pre-treatment (leukapheresis to obtain T-cells, conditioning chemotherapy to enhance CAR-T efficacy and bridging chemotherapy to stabilise disease) and administration. The base case analysis assumes that the rate of patients transitioning into the disease-free state (complete remission) is higher than, and the rate of patients transitioning into relapse health states is lower than that of the comparator. According to the ALFA-0701 phase III trial, approximately 21% of patients treated with standard chemotherapy have resistant disease (i.e., do not achieve complete remission), whereas roughly 12% treated with an anti-CD33 antibody conjugate have resistant disease. In scenario A, we conservatively assumed that 12% of CAR-T patients have resistant disease. For scenario B, given clinical evidence of CAR-T therapy having more durable remissions and better survival outcomes in similar disease indications, we assume a lower proportion (10%) of CAR-T patients with resistant disease (Cappell and Kochenderfer, 2023a).

Comparator

The SoC for untreated AML varies based on patient age, fitness, and disease characteristics. For typical patients (under 70 and fit enough to have intensive chemotherapy), the standard approach is intensive induction chemotherapy with the "7+3" regimen (7 days of cytarabine plus 3 days of an anthracycline, i.e., daunorubicin), often followed by consolidation therapy with high dose cytarabine. Recent guidelines and updates to recommendations also underscore that anthracyclines and cytarabine remain the backbone of intensive and consolidation chemotherapy (Döhner et al., 2022). If complete remission is not achieved, salvage chemotherapy or non-curative therapies are considered. There are some newer therapies added to first line AML therapy, such as gemtuzumab-ozogamicin (GO, a humanized anti-CD33 IgG4 antibody), but evidence on the is not unanimous and is limited to favourable or intermediate cytogenetic risk in disease.

For older patients (70 or older) who are often considered unfit for intensive chemotherapy, SoC includes a combination of a hypomethylating agent (azacitidine or decitabine) with venetoclax. In this analysis, we exclude this subpopulation for two primary reasons. First, although CAR T-cell therapy has shown promise in treating certain hematologic malignancies, its applicability in older populations is constrained; factors such as comorbidities and related toxicities may limit its use in older patients (Shouse, Danilov and Artz, 2022). Second, we expect a limited impact on broader economic impacts for an older population due to factors such as retirement or decreased workforce participation (Zheng et al., 2015).

There are additional therapies available for specific genetic mutations, such as FLT3 (~30% of AML patients (Daver et al., 2019)) or IDH1/IDH2 (~10% of AML patients; (Molenaar et al., 2018)) mutations. It has now become standard to incorporate FLT3 inhibitors into first-line therapy for patients with FLT3-mutant AML, in the induction and consolidation stages as well as the maintenance stage. Maintenance treatment includes post-remission therapy that aims to eliminate any remaining leukaemia cells and prevent relapse.

Given the prevalence of FLT3-mutant AML and the routine commissioning of FLT3 inhibitors, we have assumed that comparator for this analysis will be a basket of therapies, wherein 70% of patients are treated as patients with no identified specific mutations, and 30% of patients will be treated as patients with FLT3 mutation status (Daver et al., 2019). In the UK, no IDH mutation-specific treatments have been approved and are in routine use; therefore, it will be assumed that these patients are treated similar to patients with no identified specific mutations.

For intermediate- or high-risk patients who achieve remission, allogeneic stem cell transplantation (allo-SCT) is considered provided a suitable donor is identified. Given that allo-SCT can only be received after initial treatment and eligibility is a key factor for consideration, this analysis does not consider allo-SCT as a comparator, nor does it

include allo-SCT within the treatment pathway. Instead, the costs and disutilities of allo-SCT are applied to each treatment arm based on published rates of allo-SCT.

Based on the reasons outlined above, the SoC consists of:

For 70% of patients:

Induction: 7+3 regimen with cytarabine and daunorubicin

Consolidation: High dose cytarabine

Subsequent therapies: FLAG-IDA chemotherapy regimen or non-curative therapies

For 30% of patients with FLT3 mutations:

Induction: 7+3 regimen with cytarabine and daunorubicin, with quizartinib

Consolidation: High dose cytarabine, with quizartinib

Maintenance: Quizartinib only

Second-line treatment: FLAG-IDA chemotherapy regimen or non-curative therapies

Outcomes

Outcomes are based on achieving and retaining complete remission, with patients considered "functionally cured" from AML. Complete remission is associated with improved health-related quality of life, higher rates of survival, lower use of healthcare resources, and reduced risk of developing adverse events associated with chemotherapy. These patients are also expected to have improved workplace productivity and reduced carer burden.

Outcome measures that are considered include life years, QALYs, total healthcare costs and productivity losses for the patient as well as the caregiver.

Model structure

The model structure, as seen in Figure 3, follows a five-state cohort transition model, similar to existing cohort models published for AML therapies (Russell-Smith et al., 2021):

Induction: the first phase of AML treatment, aimed at achieving remission. SoC patients are given the "7+3" regimen with or without quizartinib, while CAR-T patients are administered treatment in this cycle (and undergo leukapheresis, conditioning and bridging chemotherapy). Patients are assumed to receive one round of induction therapy, and if they achieve remission, they move to complete remission state. Otherwise, they move to the refractory state. All patients have to exit the health state after one cycle.

Complete Remission (CR): this state includes the consolidation treatment, as well as maintenance treatment for SoC patients. This health state includes a tunnel state, CR I, where all SoC patients can receive consolidation treatment for 2 cycles, after which they move into CR II. Here, CAR-T patients and SoC patients without FLT3+ mutation only receive costs of disease monitoring and management in this health state. SoC patients with FLT3+ mutation receive maintenance treatment with quizartinib. Patients who do not achieve remission move into the relapse state.

Refractory: patients move to this state if they do not respond to initial therapy and do not achieve CR. Here, SoC patients receive a combination of salvage chemotherapy and non-curative therapies. CAR-T patients only receive costs of disease monitoring and management in this health state.

Relapse: patients move to this state if their disease returns after remission (CR). Here, SoC patients receive a combination of salvage chemotherapy and non-curative therapies. CAR-T patients only receive costs of disease monitoring and management in this health state.

Death: this is an absorbing state (no transition out of this state). A one-off terminal care cost is applied in this state.

The transition probabilities used for SoC and the gene therapies are shown in the matrix in Table 25.

Table 25 Transition probabilities for acute myeloid leukaemia

STANDARD OF CARE		To					
State		**Induction**	**CR I**	**CR II**	**Refractory**	**Relapse**	**Death**
From	**Induction**	0.00	0.98	0.00	0.02	0.00	0.00
	CR I	0.00	0.00	1.00	0.00	0.00	0.00
	CR II	0.00	0.00	0.96	0.00	0.04	0.00
	Refractory	0.00	0.00	0.00	0.95	0.00	0.05
	Relapse	0.00	0.00	0.00	0.00	0.94	0.06
	Death	0.00	0.00	0.00	0.00	0.00	1.00
CELL AND GENE THERAPY		To					
State		**Induction**	**CR I**	**CR II**	**Refractory**	**Relapse**	**Death**
From	**Induction**	0.00	0.99*	0.00	0.01*	0.00	0.00
	CR I	0.00	0.00	1.00	0.00	0.00	0.00
	CR II	0.00	0.00	0.96	0.00	0.04	0.00
	Refractory	0.00	0.00	0.00	0.95	0.00	0.05
	Relapse	0.00	0.00	0.00	0.00	0.94	0.06
	Death	0.00	0.00	0.00	0.00	0.00	1.00

Abbreviations: CR: complete remission.
*Note: *The transitions from induction to CR I and refractory health states differ between Scenario A and B, although this difference is not significant for up to two decimal points.*

In this analysis, HSCT is not modelled as a separate health state, given the lack of probable estimates for transitions to HSCT for patients receiving CAR-T therapy. Instead, a simplified approach is applied, wherein a proportion of SoC patients are assigned the costs and disutilities associated with HSCT. Additionally, this model accounts for "functionally cured" patients based on achieving and retaining complete remission, rather than including a separate state as per Russell-Smith et al. (2021).

The economic evaluation of gemtuzumab ozogamicin sources inputs such as remission rates, overall survival, relapse-free survival and adverse events from the ALFA-0701 phase III trial. Given that the economic evaluation assesses direct healthcare costs and QALYs for standard chemotherapy, our model borrows relevant parameters informing the health state transitions, mortality risk, health state costs, and HRQoL. For the proportion of patients receiving quizartinib, cost and utility inputs are taken from an economic

evaluation of quizartinib for patients with FLT3-ITD mutant AML (Bewersdorf et al., 2024). Inputs for the CAR-T therapy are derived from NICE submissions or publications from related disease indications with established CAR-T treatment pathways, such as ALL and mantle cell lymphoma (NICE, 2021a; Petersohn et al., 2022). All additional relevant AML parameters per disease state (direct and indirect costs, patient and carer productivity losses, utility values, and mortality risk) are in Table 26, Table 27, and Table 28.

Simplifying assumptions

We have made several simplifying assumptions in this analysis, compared to previous economic evaluations and appraisals. This was due to i) the limited availability of clinical data; ii) modelling a hypothetical treatment with less evidence of impact on treatment progression; and iii) need for increased generalisability in approach to allow for comparison with other indications.

Incidence-only population

In this analysis, we only model an incident population of AML instead of considering both prevalent and incident populations together. The population of interest is untreated AML patients, i.e., patients beginning treatment. The typical disease progression and treatment pathways vary significantly between untreated patients and patients with relapse or refractory disease. For example, prognosis for relapsed AML patients is generally poorer than for newly diagnosed patients, with lower median overall survival (Thol and Heuser, 2021). Further, treatment approaches differ between the groups; while newly diagnosed patients typically receive standard induction, relapsed patients often require salvage cytotoxic therapy or are considered for clinical trials testing pathway-targeted agents and immunotherapy-based approaches (Daver et al., 2020). Modelling only incident population allows for a more homogenous sample of patients, ensuring both inputs and outcomes remain valid for the chosen population.

Adverse events

Given previous trials and NICE submissions indicate a comparable safety profile between CAR-T and SoC patients, we take a simplified approach to modelling adverse events, focusing only on those which are potentially severe and are likely to differ between treatment groups (NICE, 2024c; Maude et al., 2018). We include the most significant adverse events associated with CAR-T therapy, which are cytokine release syndrome (CRS) and neurological events (Adkins, 2019). CRS is a systemic inflammatory response that occurs from the rapid activation of immune cells, resulting in fever, hypotension and organ dysfunction. Neurological events associated to CAR-T therapy range from mild, such as headache and confusion, to severe, such as encephalopathy and seizures.

While there are ongoing trials exploring CAR-T therapies in AML, there are no CAR-T treatments currently offered in clinical practice. Given this, this analysis assumes the safety profile of the hypothetical CAR-T to be similar to that of CAR-T therapies in similar disease indications, such as ALL and mantle cell lymphoma. Adverse event rates are derived from the ZUMA-3 trial, which evaluated brexucabtagene autoleucel in adults with relapsed or refractory B-cell ALL.

Simplification of HSCT

In existing state-transition models of AML, HSCT is typically included within the model structure as a distinct health state. This is done to reflect the transition to transplantation from other health states, as well as incorporate transplant-related mortality and long-term survival probabilities for patients who undergo HSCT. We take a simplified approach in this analysis in order to limit the number of assumptions used for determining transitions between health states, specifically for the hypothetical CGT.

In our analysis, a proportion of patients are assigned costs and disutilities related to HSCT. For SoC patients, this is based on state-specific HSCT utilisation for patients in complete remission (8.4%), refractory (19.1%) and relapse (14.4%) health states, as reported in ALFA-0701 (Russell-Smith et al., 2021). Patients undergoing HSCT have a high risk of graft-versus-host disease (GVHD), a potentially life-threatening complication; we further model a proportion of patients to receive the costs and disutilities associated with GVHD, obtained from the NICE appraisal of midostaurin for untreated AML (NICE, 2017).

Given that the relationship between CAR-T therapy and HSCT is still subject to ongoing research and the use of CAR-T in AML is still evolving, we apply certain restrictions in the modelling of HSCT and related complications for CAR-T patients. In scenario A, we model HSCT and related complications for CAR-T patients in the relapse health state, in line with HSCT utilisation estimates for current antibody-based therapy for AML, derived from ALFA-0701 (Russell-Smith et al., 2021). In our more optimistic scenario, scenario B, we assume that CAR-T patients do not undergo HSCT treatment. This is because there is still uncertainty on whether CAR-T therapy and HSCT are complementary or competitive treatments for hematologic malignancies, especially given increasing evidence that CAR-T therapy provides durable remissions without the need for subsequent transplantation (Goldsmith et al., 2022; Cappell and Kochenderfer, 2023b).

Parameter values for AML

Table 26 Parameter values for acute myeloid leukaemia

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
EPIDEMIOLOGY	Mean age at baseline (years)	61.2	Russell-Smith et al. (2021)
	Proportion of female	50.93%	Russell-Smith et al. (2021)
	Incident AML population	2945	Cancer Research UK (2019)
	Population eligible for CAR-T (Scenario A)	2397	Assumption, 81.4% of patients receive CAR-T based on TA975
	Population eligible for CAR-T (Scenario B)	2945	Assumption, all patients receive CAR-T
PATIENT UTILITIES	Patient utility — Induction	0.66	Russell-Smith et al. (2021)
	Patient utility — CR I	0.74	Russell-Smith et al. (2021)
	Patient utility — CR II	0.74	Russell-Smith et al. (2021)
	Patient utility — Refractory	0.57	Russell-Smith et al. (2021)
	Patient utility — Relapse	0.57	Russell-Smith et al. (2021)
	Patient utility — Death	0.00	
HEALTH-STATE COSTS FOR CGT[1]	Healthcare costs — Induction	£28,453.70	TA1013
	Healthcare costs — CR I	£511.14	TA1013
	Healthcare costs — CR II	£511.14	TA1013
	Healthcare costs — Refractory	£2,464.01	TA1013
	Healthcare costs — Relapse	£2,464.01	TA1013
	Healthcare costs — Death	£0.00	

HEALTH-STATE COSTS FOR SOC[1]	Healthcare costs — Induction	£10,078.81	TA1013
	Healthcare costs — CR I	£3,538.11	TA1013
	Healthcare costs — CR II	£6,209.09	TA1013
	Healthcare costs — Refractory	£5,803.97	TA1013
	Healthcare costs — Relapse	£5,803.97	TA1013
	Healthcare costs — Death	£0.00	
ONE-OFF COSTS AND DISUTILITIES[1]	Costs — HSCT	£39,257	TA1013
	Disutilities — HSCT	-0.04	Sung et al. (2003)
EVENT PROBABILITIES	Probability — HSCT (SoC: CR II)	8.38%	Tokaz et al. (2023)
	Probability — HSCT (SoC: refractory)	19.15%	Russell-Smith et al. (2021)
	Probability — HSCT (SoC: relapse)	14.37%	Russell-Smith et al. (2021)
	Probability — HSCT (CGT: relapse) (Scenario A)	9.58%	Russell-Smith et al. (2021)
	Probability — HSCT (CGT: relapse) (Scenario B)	0.00%	Assumption
	Probability — GVHD (SoC; CGT only for Scenario A)	39%	TA523
	Probability — CRS (CGT only)	24%	ZUMA-3
	Probability — Neurologic events (CGT only)	25%	ZUMA-3
ADVERSE EVENTS[1]	Costs — CRS	£9,094.81	TA893
	Costs — Neurologic events	£3,284.82	TA893
	Costs — GVHD	£61,023.63	TA1013
	Disutilities — CRS	-0.03	Howell et al. (2020)
	Disutilities — Neurologic events	-0.04	TA893
	Disutilities — GVHD	-0.085	TA1013
DEATH COST[1]	End-of-life care	£6,948.31	Russell-Smith et al. (2021)

1. All costs are inflated to and reported in 2024 GBP

Table 27 Productivity effects for acute myeloid leukaemia

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
GENERAL POPULATION INPUTS	Retirement age	68	(NICE, 2024)
	Days of work, per year	253.25	
	Hours of work, per day	6.36	Average working hours per week (ONS, 2024a)
	Value of working time: lost production	£18.93	Average hourly wage (ONS, 2024a)

	Average employment rate amongst AML patients	54%	(Samadi et al., 2017)
PATIENT PRODUCTIVITY LOSS	Absenteeism — Induction	72.78%	(Pandya, 2024)
	Absenteeism — CR I	56.96%	(Pandya, 2024)
	Absenteeism — CR II	56.96%	(Pandya, 2024)
	Absenteeism — Refractory	70.97%	Assumed the same as relapse, based on (Pandya, 2024)
	Absenteeism — Relapse	70.97%	(Pandya, 2024)
	Absenteeism — Death	100.00%	Assumption
CARER PRODUCTIVITY LOSS	Absenteeism — Induction	83.21%	(Pandya, 2024)
	Absenteeism — CR I	79.56%	(Pandya, 2024)
	Absenteeism — CR II	79.56%	(Pandya, 2024)
	Absenteeism — Refractory	83.78%	Assumed the same as relapse, based on (Pandya, 2024)
	Absenteeism — Relapse	83.78%	(Pandya, 2024)
	Absenteeism — Death	0.00%	Assumption

1. All costs are inflated to and reported in 2024 GBP

Table 28 Mortality for acute myeloid leukaemia

	PARAMETER	VALUE	HAZARD RATIO - AML
DEATH RISK	Retirement age	Hazard ratio — AML	1.35

Steady-state results for AML

Table 29 Steady-state (annual) results, AML, scenario A

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£2,652,696,761	£2,398,050,359	£254,646,402
	Systems	-£163,220,844	-£573,613,821	£410,392,977
	National economy	-£1,845,716,235	-£1,841,458,613	-£4,257,622
HEALTH OUTCOMES	QALYs	37,896	34,258	3,638
	Life years	48,563	48,394	169

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Table 30 Steady-state (annual) results, AML, scenario B

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£3,265,945,807	£2,946,007,813	£319,937,994
	Systems	- £158,271,105	- £704,685,283	546,414,178
	National economy	- £2,268,737,755	- £2,262,234,168	- £6,503,587
HEALTH OUTCOMES	QALYs	46,656	42,086	4,571
	Life years	59,711	59,452	259

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Comparison of results to similar evaluations

This analysis considers a hypothetical CAR-T therapy designed to modify disease progression in AML. To date, no CAR-T therapies have received regulatory approval for AML. The proposed CGT can be conceptually aligned with other disease-modifying treatments. This includes azacitidine, which is routinely used in patients deemed unsuitable for intensive chemotherapy. Azacitidine is approved for use in selected AML populations, including older adults and patients with high-risk myelodysplastic syndromes. Additionally, for patients with FLT3+ mutations, targeted therapies like midostaurin offer improved outcomes when used in combination with intensive chemotherapy (Tremblay et al., 2018).

We modelled one prevalent patient over a lifetime horizon, to compare results with existing studies exploring the impact of treatments in AML whose effect is most similar to CGT. We also include the cost of the CAR-T therapy in this analysis to align our results with the methods used in the other studies.

For comparison, we selected two relevant studies: 1) Coyle and Villeneuve, 2020, which is an economic evaluation of azacitidine compared to SoC for treating high-risk patients with AML in a Canadian public healthcare system and 2) Tremblay et al., 2018, a cost-effectiveness analysis of addition of midostaurin to standard of care for newly diagnosed FLT3+ AML patients in the UK.

In Table 31 and Table 32, we present per-patient discounted outcomes for scenarios A and B alongside the results from the selected studies. For the azacitidine comparison, we do not include a cost comparison, as the reference study (Coyle and Villeneuve, 2020) was conducted in the Canadian healthcare setting, where differences in unit costs, resource use patterns, and reimbursement mechanisms limit the transferability of cost estimates to our UK-specific context.

While we include costs for the midostaurin study (Tremblay et al., 2018), this comparison has a few limitations and should be interpreted with caution. Midostaurin is an oral targeted therapy used alongside standard chemotherapy, whereas CAR-T therapy is a complex, personalised, hospital-delivered treatment with high upfront costs. The two interventions have fundamentally different cost structures. In addition, the midostaurin analysis uses 2017 prices, and while inflation adjustments were made, differences in drug pricing, care pathways, and follow-up costs remain.

Table 31 Azacitidine evaluation comparison

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS (1.5%)	INCREMENTAL GAIN DISCOUNTED LYS (1.5%)
(Coyle and Villeneuve, 2020; Udeze et al., 2023)	Canada	Azacitidine versus SoC	0.10	0.17
Current analysis (Scenario A-Scenario B)	UK	CGT versus SoC	1.43	0.06

Table 32 Midostaurin evaluation comparison

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS (3.5%)	INCREMENTAL GAIN DISCOUNTED LYS (3.5%)	INCREMENTAL GAIN DISCOUNTED COSTS (3.5%)
(Tremblay et al., 2018; Udeze et al., 2023)	UK	Midostaurin + SoC versus SoC	1.47	1.67	£65k
Current analysis (Scenario A-Scenario B)	UK	CGT versus SoC	1.11	0.05	£186k

The QALYs in our analysis are broadly comparable to those reported in the comparator studies, with greater benefit observed for CAR-T, which is consistent with its curative potential. The differences in QALYs in our analysis relative to selected studies may reflect the lack of data for CAR-T in AML and subsequent conservative survival assumptions we have taken. Despite demonstrating a survival advantage in specific patient groups, neither azacitidine nor midostaurin is curative and they both require ongoing or multi-phase administration. In contrast, CAR-T therapy may represent a transformative therapeutic approach in this indication, offering the potential for a more durable or potentially curative effect with a single administration. The negligible difference in life years is likely due to the shorter time horizon in our analysis, which may not fully capture the long-term survival benefits associated with CGT.

D. Beta thalassaemia case study details

Beta thalassaemia (BT) is among the most common autosomal recessive disorders globally (NICE, 2024a), requiring the inheritance of two mutated gene copies, one from each parent. These mutations result in either reduced (β^+) or absent (β^0) production of beta-globin chains, essential components of adult haemoglobin (NICE, 2024a). Consequently, haemoglobin synthesis is impaired, and unpaired alpha-globin chains accumulate in red blood cell (RBC) precursors, forming aggregates that cause mechanical and oxidative damage.

The severity of BT is determined by the specific mutation in the beta-globin gene and is broadly classified into (NICE, 2024a):

- BT major: haemoglobin production is so reduced that normal growth, development, and health-related quality of life (HRQoL) can only be achieved by regular RBC transfusion

- BT intermedia: although haemoglobin production is decreased, the levels are sufficient to support growth and development, and regular transfusions are not strictly necessary.

However, disease severity exists on a continuum, with overlapping features between BT major and intermedia. An alternative classification, used in this analysis, follows the Thalassemia International Federation (TIF) guidelines, which categorise patients based on transfusion requirements (Thalassaemia Internation Federation, 2021):

- Non-transfusion dependent beta-thalassaemia (NTDT)

- Transfusion-dependent beta-thalassaemia (TDT)

TDT is the most severe form and is characterised by chronic, life-threatening anaemia that necessitates lifelong, regular RBC transfusions (Thalassaemia Internation Federation, 2021). Due to the need for ongoing transfusions, patients must also undergo lifelong iron chelation therapy (ICT), which is associated with substantial healthcare resource utilisation and costs.

Both the disease itself and complications arising from iron overload contribute to various comorbidities specifically linked to TDT (NICE, 2024a). Life expectancy for individuals with TDT remains significantly lower than the general population, with estimates indicating that 40% of patients in the UK die before reaching the age of 50 (Weidlich, Kefalas and Guest, 2016). Jobanputra et al., (2020) reported the mean age of death for patients with TDT as 55.0 years, while a separate study found an even lower mean age of death at 43.9 years.

TDT also profoundly affects patients' ability to perform daily activities and engage in family and social life (NICE, 2024a). A multi-national prospective longitudinal study evaluating HRQoL using the EQ-5D-5L and work productivity among adult patients with TDT reported that most patients experienced problems with pain, anxiety, or depression, and the ability to conduct daily activities (Li et al., 2022a). However, evidence suggests that the EQ-5D-5L descriptive system lacks content validity, and the derived health utility index score may not fully represent the burden of disease in BT, hence it may underestimate the overall burden (Boateng-Kuffour et al., 2024).

The impact of TDT goes beyond the individual, resulting in impacts on carer burden, work productivity, and employment outcomes. Patients with TDT need a considerable amount of time off from education and work to manage their condition. This is due to time spent travelling to and from medical appointments and time spent at appointments (Li et al., 2022a).

Patients with TDT both experience absenteeism and presenteeism, 19.5% and 34.4% respectively (Li et al., 2022a). In addition, only 65.4% of patients with TDT are employed either part-time or full-time (Li et al., 2022a), below the general population average of 75.5% (ONS, 2024a).

Methods

Scenarios

Table 33 below outlines the differences between the conservative scenario A and the more optimistic scenario B. The primary difference is the population that receives the CGT. Scenario A is identical to the population in the NICE appraisal of exa-cel, specifically patients over the age of 12 who have TDT who are fit for transplant and without a human leukocyte antigen (HLA)-matched sibling donor (NICE, 2024a). Scenario B considers the complete TDT population, assuming a larger pool of patients may benefit from a CGT. The populations are shown in Table 33.

The other difference between the scenarios is the effectiveness of the CGT, namely the proportion of patients reaching the state of transfusion independent (TI). This is as described in 'Dropping the TR health state' sub section below, where in scenario B, 100% achieve TI and in scenario A, 92.6% achieve TI, with the rest being transfusion dependent (TD).

Table 33 Beta thalassaemia scenarios

PARAMETER	SCENARIO A	SOURCE / EXPLANATION A	SCENARIO B	SOURCE / EXPLANATION B
PREVALENT POPULATION ELIGIBLE FOR TREATMENT	352	In line with the base case population in the NICE evaluation of exa-cel (NICE, 2024a). Patients who are TDT, fit for the procedure, and don't have a matched donor	920	The entire TDT population being eligible for the treatment.
INCIDENT POPULATION ELIGIBLE FOR TREATMENT	8.18	Estimation of the incident population size based on the eligibility as above (NICE, 2024a).	21.4	Estimation of the incident population size based on the eligibility as above.
PROPORTION ACHIEVING TI	0.926	In line with the NICE evaluation of exa-cel (NICE, 2024a), 92.6% of patients achieve TI.	1	All patients achieve TI

Population

The modelled population differs across the two scenarios in our analysis, but both focus on patients aged 12 and older with TDT. This age threshold and disease definition align with the population used in the NICE appraisal of exa-cel (NICE, 2024a) and the Institute for Clinical and Economic Review (ICER) appraisal of beti-cel (Beaudoin et al., 2022).

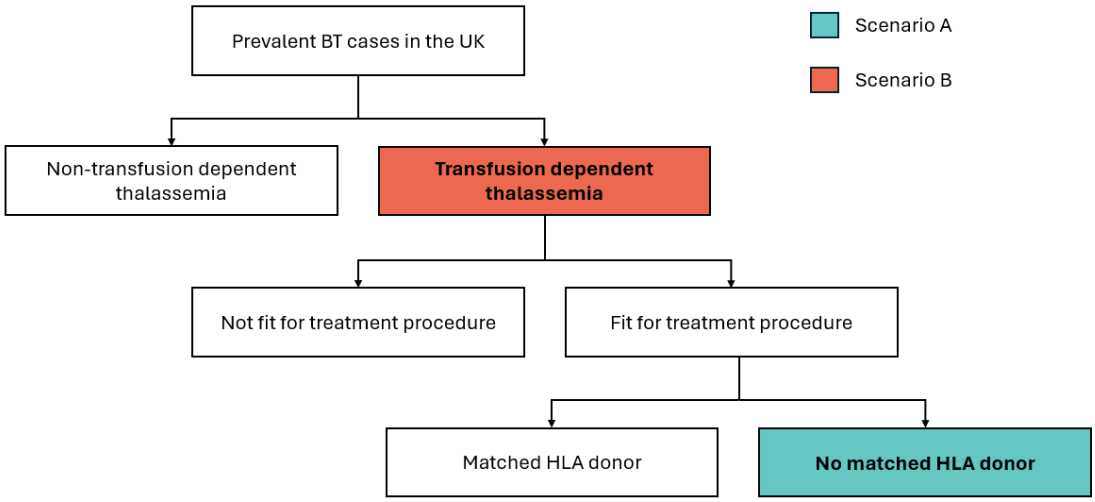
In the NICE appraisal of exa-cel, the mean patient age was 21 years, with 52.1% identifying as female. The ICER appraisal of beti-cel reported a similar mean age of 22 years. Based on assumptions described in the next section, we used a starting age of 25 years for our analysis.

It's estimated that there are 1,210 patients with BT aged 12 years or older in the UK (NICE, 2024a), and 76% of patients are considered to have TDT (NHS, 2014), defined as requiring greater than or equal to eight RBC transfusions per year. Using this estimate, the prevalent population of patients with TDT in the UK is approximately 920. In the NICE appraisal of exa-cel, the population was further restricted to those who are fit for transplant and without a human leukocyte antigen (HLA)-matched sibling donor (NICE, 2024a). This results in a population size of 352 patients with TDT without an HLA-matched sibling donor. Figure 6 illustrates the epidemiological cascade described above.

We were not able to identify any sources reporting the incidence of BT. The 'Sickle Cell and Thalassemia Screening: Data Report 2019 to 2020' combines data on both sickle cell and thalassaemia screening outcomes (NHS England, 2022). It provides data on carrier rates, prenatal diagnoses, and screening coverage; however, the data is not separated into specific case counts for BT or other variants.

Therefore, to estimate the incident population, we divided the size of the prevalent, treatment-eligible population by the average disease duration. This approach assumes a constant age distribution among patients with BT. Average disease duration was estimated by subtracting the age of inclusion (12 years) from the life expectancy of individuals with TDT in the UK, 55 years, resulting in an average disease duration of 43 years.

Figure 6 Beta thalassaemia epidemiological cascade, recreated from (NICE, 2024a)



Intervention

The intervention evaluated in this analysis is a hypothetical one-time gene or cell therapy (CGT) that aims to address the underlying cause of beta-thalassaemia (BT), leading to a transfusion-independent (TI), disease-free state. While not representing a specific marketed therapy, its assumed effectiveness and characteristics are informed by clinical data for exa-cel and beti-cel (Beaudoin et al., 2022; NICE, 2024a).

Comparator

In the UK, TDT is treated by a regular programme of RBC transfusions, administered approximately every 2-5 weeks (NICE, 2024a). This is to treat anaemia in patients with BT, as the disease causes a drop in RBC count (NHS, 2022), helping to reduce anaemia, increase haemoglobin levels and improve health.

However, frequent RBC transfusions result in iron accumulation and overload, which is associated with TDT complications (NICE, 2024a). This means patients require their iron burden to be monitored alongside treatment with ICT. Due to the nature of ICT, patients must be constantly monitored and managed, increasing the burden of treatment on clinicians, patients, and caregivers.

Allogenic HSCT (allo-HSCT) can be curative of BT and is a potential treatment option for some patients. It involves replacing the bone marrow stem cells in patients with stem cells from an HLA-matched sibling donor (NHS England, 2023). Following a recommendation from NHS England's clinical priorities advisory group, it has recently become available on the NHS for those over 18 years old (NHS England, 2023).

However, it is generally restricted to paediatric patients who have a matched sibling donor (Kansal et al., 2021). Clinical expert opinion from the NICE appraisal of exa-cel suggests that it's only given to patients who are 9 years and younger (NICE, 2024a). Furthermore, in the USA, allo-HSCT is only performed in children under the age of 14 years of age. This is because allo-HSCT carries a significant risk of transplant-related mortality that increases with age, and serious complications such as graft versus host disease and graft rejection (NICE, 2024a).

Furthermore, the lack of compatible donors is a limiting factor for allo-HSCT, with only around 25% of patients having access to a compatible donor (NICE, 2024a; Beaudoin et al., 2022). In the appraisal of exa-cel, the population was restricted to transfusion-dependent BT patients 12 years of age or older for whom an HLA-matched related allo-HSCT donor is not available (NICE, 2024a).

For the reasons outlined above, we are not considering allo-HSCT as a comparator. The SoC is therefore frequent RBC transfusions, ICT, as well as the monitoring and management of complications.

Outcomes

Outcomes are based on achieving TI, with no waning treatment effect. This eliminates the need for RBC transfusions, reduces the complications associated with RBC transfusions, and lowers the risk of developing complications related to iron levels.

Exa-cel enables some patients to achieve a disease-free state; 92.6% achieve TI with exa-cel, while the remaining 7.4% achieve transfusion reduction (NICE, 2024a). Beti-cel is another potentially curative gene therapy (Beaudoin et al., 2022), involving intravenous delivery following myeloablative conditioning with chemotherapy; data suggests 90.2% achieve TI following treatment with Beti-cel (Beaudoin et al., 2022).

Being in the disease-free TI state will contribute to reduced healthcare resource utilisation, improved health-related quality of life and survival, as well as improved work-related outcomes and reduced carer burden. All of which will be captured and measured.

Model structure

The model structure follows a cohort three-state transition mode, shown in Figure 4:

Transfusion dependent (TD): the most serious form of BT representing TDT. Patients require regular RBC transfusions for life, ICT therapy, increased risk of mortality, lower HRQoL and decreased workplace productivity.

Transfusion independent (TI): represents a disease-free state, with a slightly higher mortality risk compared to the general population.

Dead

A version of this model structure, based on transfusion status, has been used previously in the economic evaluation of both CGT therapies in BT as well as for non-CGT therapies in BT (NICE, 2024a; Beaudoin et al., 2022; CDA-AMC, 2021; Kansal et al., 2021).

A very similar model structure is used in the ICER evaluation of beti-cel (Beaudoin et al., 2022). In the NICE appraisal of exa-cel, a similar structure is also applied with an additional health state, namely a transfusion reduction (TR) state. This is to capture those patients who don't achieve TI but experience a significant reduction in RBC transfusion frequency (NICE, 2024a). Exclusion of this state here is explained in the "simplifying assumptions" section below.

Patients who are TD are at risk of a series of complications based on their transfusion status and a series of iron levels: serum ferritin, myocardial T2, and liver iron concentration (NICE, 2024a). For each of these iron levels, patients who are TD are distributed between low, medium, and high levels, which determines their risk of experiencing certain complications. The distribution remains constant through the entire time horizon of the model.

Cardiac complications are based on myocardial T2 levels, and liver complications are based on liver iron concentration levels. The risks of developing diabetes or hypogonadism were calculated as a function of age, SF level, and myocardial T2 level. The risk of complications for patients who achieve TI is assumed to be the same as for the general population.

The parameter values informing the health state costs, risk of mortality, HRQoL, and productivity effects were primarily sourced from the NICE appraisal of exa-cel (NICE, 2024a). Where alternative sources are used, these are outlined and explained. The full list of parameters used are in Table 34, Table 35, and Table 36.

Simplifying assumptions

When modelling patients with BT we have made a few simplifying assumptions in comparison to previous economic evaluations and HTA appraisals. This is to increase the generalisability of the approach, in line with the generalisable model template developed in R.

Dropping the TR health state

We have used a slightly simplified model structure compared to the NICE evaluation of exa-cel, without the TR state. In the NICE evaluation, 92.6% achieved TI, and 7.4% TR, with no patients remaining in the TD state.

When we model the two base case scenarios (A&B), we vary the proportion achieving TI. In the more optimistic scenario, we assume all patients receiving the intervention will achieve TI. In the other, we assume a small proportion remain in TD, despite receiving the CGT. We do not expect this to have a significant impact on the results due to the relatively small numbers who are TR.

Furthermore, many parameters for TR state in the NICE evaluation of exa-cel, are selected as a midpoint between TD and TI. This applies to parameters including but not limited to the health state costs, caregiver's disutility, and absenteeism and presenteeism values for patients and caregivers. On this basis and to simplify the structure of the model where possible, we excluded this health state.

No iron normalisation period or treatment phase

In three evaluations of CGTs found in the literature (Beaudoin et al., 2022; Kansal et al., 2021; NICE, 2024a), there was a period known as the 'iron normalisation' period following CGT treatment. During this time, patients' iron levels gradually adjust until they reach a normal, healthy range, at which point RBC transfusions are no longer required. In NICE's evaluation of exa-cel, this period spans three years, following a one-year treatment phase. Meanwhile, in the ICER evaluation of beti-cel, the iron normalisation period was set at five years.

Our model follows a simplified approach, whereby we apply an upfront utility loss, representing the HRQoL impact of treatment with a CGT, based on exa-cel and beti-cel. In the CGT arm, the proportion of patients who achieve TI, start and remain in that state (until death). This is rather than this being proceeded by an iron normalisation period. In the SoC group, patients will start and stay in the TD state with the associated distribution of iron levels.

This simplification was made on the basis that in the iron normalisation period, the outcomes would offset one another, if not be exceeded in the SoC arm. This means the assumption is overall conservative. The consideration of these outcomes would be more important for a HTA style evaluation or budget impact analysis and are less relevant to our analysis.

TDT complications simplification

The TDT-related complications are health issues associated with TD and the administration of regular RBC transfusion. Whilst essential, regular RBC transfusions lead to a range of complications due to a combination of the underlying disease and treatment. These complications include, but are not necessarily limited to: cardiac, liver, osteoporosis, diabetes and infertility (NICE, 2024a). They impact health state utility, costs, and (some) mortality.

In our analysis, these are captured and treated as adverse events, associated with a cost and impact on utility. Monthly event rates are estimated and used to capture the proportion of patients who suffer from complications. In the NICE evaluation of exa-cel, these are assumed to last for the remainder of the modelled period (NICE, 2024a). However, since we are treating them as adverse events in our analysis, we do not make this same assumption, with the events occurring at fixed event rates. This likely underestimates the full cost and humanistic burden of such complications.

Complication-specific disutility and costs are applied for the patient's suffering complications. An increased mortality risk associated with complications is not directly accounted for by those who suffer the complications. However, this is reflected in the standardised mortality ratio (SMR) for TI and TD. Some of the data in the NICE analysis is redacted or not reported simply as monthly event rates, and in some cases, we use alternative sources to generate estimations. We account for the occurrence of complications as far as possible, but we likely underestimate the full burden in this study.

Parameter values for BT

Table 34 Parameter values for beta-thalassaemia

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
EPIDEMIOLOGY	Mean age at baseline (years)	25	(NICE, 2024a)
	Proportion of female	52.1%	(NICE, 2024a)
	Scenario A prevalent population	352	Based on data from (NHS, 2020; NICE, 2024a)
	Scenario A incident population	8.18	Calculated based on the size of the prevalent TDT population and average life expectancy of TDT (55 years) (NICE, 2024a)
	Scenario B prevalent TDT population	920	Based on data from (NHS, 2020; NICE, 2024a)
	Scenario B incident TDT population	21.39	Calculated based on the size of the prevalent TDT population and average life expectancy of TDT (55 years) (NICE, 2024a)
PATIENT UTILITIES	Patient utility — TI	0.93	(Matza et al., 2020)
	Patient utility — TD	0.73	(Matza et al., 2020)
	Patient utility — Death	0.00	
HEALTH-STATE COSTS[1]	Monthly healthcare costs — TI	£38.14	(NICE, 2024a)
	Monthly healthcare costs — TD	£1,780.65	Calculation based on (NICE, 2024a), includes cost of RBC transfusion and iron chelation
ONE OF COSTS AND DISUTILITIES[1]	Costs - Acquisition cost of CGT	£1,651,000	Reported list price of exa-cel (NICE, 2024d)
	Costs — Healthcare costs associated with CGT	£37,033.24	Calculated based on the costs reported in NICE (2024a), excluding mobilisation cost
	Disutility — Treatment with CGT in transplant year	0.31	Based on (NICE, 2024a; Matza et al., 2020)
CGT EFFECTIVENESS	The proportion of patients achieving TI in scenario A	0.926	In line with the effectiveness of exa-cel, with 92.6% achieving TI

	The proportion of patients achieving TI	1	An assumption based on the effectiveness of exa-cel with 92.6% achieving TI, 7.4% achieving TR and 0% with TD
TDT COMPLICATIONS EVENT RATES	Monthly event rate — cardiac complications - TD	0.00101	Calculated based on (Pepe et al., 2018) and distribution of myocardial T2 iron levels (Shah et al., 2021)
	Monthly event rate — cardiac complications - TI	0.00025	Calculated based on (Pepe et al., 2018) and distribution of myocardial T2 iron levels (Shah et al., 2021)
	Monthly event rate — liver complications - TD	0.00118	Calculated based on (Angelucci et al., 2002; NICE, 2024a) and distribution LIC (Shah et al., 2021)
	Monthly event rate — liver complications - TI	0.0000417	Calculated based on (Angelucci et al., 2002; NICE, 2024a) and distribution LIC (Shah et al., 2021)
	Monthly event rate — Osteoporosis - TD	0.0053	Calculated taking the incident rate average across all age cohorts (Hippisley-Cox and Coupland, 2009) and increased risk associated with TD (NICE, 2024a)
	Monthly event rate — Osteoporosis - TI	0.000195	Calculated taking the incident rate average across all age cohorts (Hippisley-Cox and Coupland, 2009)
	Monthly event rate — Diabetes - TD	0.0446	Calculated using relative risk values (Beaudoin et al., 2022), the annual risk of diabetes at normal iron levels (NICE, 2024a), and the distributions of serum ferritin and myocardial T2 (NICE, 2024a)
	Monthly event rate — Diabetes - TI	0.0070	Calculated using the annual risk of diabetes at normal iron levels (NICE, 2024a)
ADVERSE EVENTS[1]	Costs — Cardiac complications	£684.71	The monthly cost of cardiac complications (Karnon et al., 2012)
	Costs — Liver complications	£283.67	(NICE, 2024a)
	Costs — Osteoporosis	£756.18	The monthly cost of osteoporosis (Hernlund et al., 2013)
	Costs — Diabetes	£531.79	The monthly cost of diabetes (Karnon et al., 2012)
	Costs — Infertility	£1,520.25	Calculated using the cost of IVF weighted by the proportion of females, and an ongoing cost of infertility (NICE, 2024a)
	Disutility — Cardiac complications	0.11	(Karnon et al., 2012)
	Disutility — Liver complications	0.11	(Tsochatzis, Bosch and Burroughs, 2014)
	Disutility — Osteoporosis	0.08	(NICE, 2024a)
	Disutility — Diabetes	0.06	(Jalkanen et al., 2019)
	Disutility — Infertility	0.06	(NICE, 2024a)
	Costs — Cardiac complications	£684.71	The monthly cost of cardiac complications (Karnon et al., 2012)

1. All costs are inflated to and reported in 2024 GBP.

Table 35 Productivity effects for beta-thalassaemia

	PARAMETER	VALUE	REFERENCES / NOTES
GENERAL POPULATION INPUTS	Retirement age	68	(NICE, 2024)
	Days of work, per year	253.25	
	Hours of work, per day	6.36	Average working hours per week (ONS, 2024a)
	Value of working time: lost production	£37,430	Median salary UK (ONS, 2024c)
	Average employment rate amongst general population	75.4%	(ONS, 2024a)
	Average employment rate amongst TDT patients	65.4%	(Li et al., 2022b)
PATIENT PRODUCTIVITY LOSS	Productivity losses — TI	0%	Assumed to be the same as general population
	Productivity losses — TD	41.7%	Productivity losses due to absenteeism and presenteeism (Li et al., 2022b)
CARER PRODUCTIVITY LOSS	Productivity losses — TI	0%	No caregiver responsibilities assumed for TI
	Productivity losses — TD	36%	Productivity losses due to absenteeism and presenteeism (Shah et al., 2021)
	Caregiving up to age	26	An assumption used in (NICE, 2024a) that caregiving is only needed for patients below the age of 26

Table 36 - Mortality for beta-thalassaemia

	PARAMETER	VALUE	REFERENCES / NOTES
DEATH RISK	SMR — TI	1.25	SMR is applied to age-specific probability of death from UK national life tables (ONS, 2024e). The SMR value is an assumption, used in NICE (2024a), that TI carries a slightly higher mortality risk than the general population
	SMR - TD	5	SMR is applied to age-specific probability of death from UK national life tables (ONS, 2024e).
DEATH COST[1]	End-of-life care	£13,576	(NICE, 2024a)

1. All costs are inflated to and reported in 2024 GBP

Steady-state results for BT

Table 37 Steady-state (annual) results, beta-thalassaemia, scenario A

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£28,110,345	£16,677,238	£11,433,107
	Systems	-£2,229,143	-£7,949,806	£5,720,663
	National economy	-£2,226,260	-£5,623,107	£3,396,847
HEALTH OUTCOMES	QALYs	401	238	163
	Life years	437	328	109

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Table 38 Steady-state (annual) results, beta-thalassaemia, scenario B

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£76,068,556	£43,600,623	£32,467,933
	Systems	-£4,530,988	-£20,783,808	£16,252,820
	National economy	-£5,048,057	-£14,700,933	£9,652,876
HEALTH OUTCOMES	QALYs	1086	622	464
	Life years	1169	858	311

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Comparison of results to similar evaluations

The analysis is not specific to any CGT currently available on the market; its effectiveness and characteristics are primarily informed by evidence related to exa-cel (NICE, 2024a). The therapy involves a single, one-time dose intended to address the underlying cause of BT. To enable comparison with other studies, we modelled one prevalent patient over a lifetime horizon, undiscounted, and discounted for scenarios A and B. This is to align our results with the analytical methods used in the other studies.

We identified three relevant studies for comparison in the BT case study (Udeze et al., 2023; Kansal et al., 2021; Beaudoin et al., 2022). Due to redactions in the NICE appraisal of exa-cel, we could not include its results in our comparison. All the studies compare a CGT to SoC, which involves frequent RBC transfusions and iron chelation therapy. This is in line with the SoC used in our analysis.

One study is an abstract outlining an economic evaluation of exa-cel for treating patients with TDT from the US payer and societal perspective (Udeze et al., 2023). A comparison to our results is seen on Table 39. The incremental gain in discounted QALYs is comparable to our analysis. However, the incremental gain in undiscounted LYs is much larger in the Udeze et al. (2023) study.

Table 39 Exa-cel evaluation comparison

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS (3%)	INCREMENTAL GAIN UNDISCOUNTED LYS
(Udeze et al., 2023)	US	Exa-cel versus SoC	8.5-8.8	16.1-18.7
Current analysis (Scenario A-Scenario B)	UK	CGT versus SoC	6.79-7.37	9.19-9.99

The CGT considered in our analysis also shares characteristics with beti-cel, the therapy assessed in two of the economic evaluations (Kansal et al., 2021; Beaudoin et al., 2022). NICE did not recommend beti-cel due to insufficient evidence of cost-effectiveness and limited clinical trial data (Staines, 2021; NICE, 2021b). Although it initially received marketing authorisation in the EU in 2019, it was subsequently withdrawn by the marketing authorisation holder in March 2022 (EMA, 2019). Beti-cel received FDA approval in March 2022 for treating adult and paediatric patients with BT who require regular RBC transfusions (FDA, 2022).

Table 40 presents a comparison of our results. Both CGT and SoC show higher undiscounted QALYs in our analysis compared to the two beti-cel evaluations. Nonetheless, the incremental QALY gains in our model are similar, falling between those reported by Kansal et al. (2021) and Beaudoin et al. (2022) for both scenarios A and B.

Table 40 Beti-cel evaluation comparison

SOURCE	SETTING	INTERVENTION	TOTAL QALYS	INCREMENTAL GAIN (QALYS)	TOTAL LIFE YEARS	INCREMENTAL GAIN (LIFE YEARS)
(Beaudoin et al., 2022)	US	Beti-cel	37.24	14.10	49.19	10.83
		SoC	23.14		38.36	
(Kansal et al., 2021)	US	Beti-cel	40.82	17.99	52.97	13.78
		SoC	22.83		39.19	
Current analysis (Scenario A)	UK	CGT	44.92 QALYs	16	50.02	9.19
		SoC	28.92 QALYs		40.83	
Current analysis (Scenario B)	UK	Gene therapy with SoC	46.29 QALYs	17.37	50.82	9.99
		SoC only	28.92 QALYs		40.83	

Overall, the comparisons indicate that the disease model component of our analysis yields results consistent with those from other economic evaluations of similar interventions. As all comparator studies adopt a U.S. perspective, we did not include a direct cost comparison, as differences in healthcare systems would limit the relevance of such a comparison from a UK perspective.

E. Alzheimer's disease case study details

Alzheimer's Disease (AD) is an irreversible and neurodegenerative brain condition. The clinical course is characterised by significant and progressive cognitive decline, from normal cognition to Mild Cognitive Impairment (MCI) due to AD, followed by increasingly severe AD-dementia (Davis et al., 2018).

Alzheimer's is the most common form of dementia (Davis et al., 2018). Dementia incidence is on the rise, and recent estimates project that by 2040, there will be 1.7 million dementia cases in England and Wales (Chen et al., 2023). Research suggests that there are inequalities in dementia associated with social deprivation and demographic factors. For example, the largest increase in dementia cases have been observed among people with lower education levels (Chen et al., 2023). Further, Black and South Asian populations living in the UK experience higher rates of dementia and are more likely to be diagnosed at a younger age and die earlier from dementia (Alzheimer's Research UK, 2023).

Alzheimer's disease has significant implications for patient and caregiver quality of life. The progressive reduction in patients' independence and quality of life subjects caregivers to increased emotional distress, poor mental and physical well-being, decreased workplace productivity, and loss of earnings and savings (Herring et al., 2021; Robinson et al., 2020).

Healthcare costs are estimated to only make up 14% of total AD costs, whereas 77% of total AD costs are spent on social care and unpaid care (Carnall Farrar, 2024). The economic burden of dementia has been found to more substantially impact the social care sector than the healthcare sector, and increases with the severity of dementia (Wittenberg et al., 2019).

Alzheimer's disease also has substantial negative effects on patient and caregiver productivity. Often only caregiver productivity costs are considered, given that the affected patient population is often close to or past retirement age (Robinson et al., 2020). Research has found that caregiver time often represents the largest resource use component related to AD (Robinson et al., 2020). Data suggests, however, that higher disease severity is also associated with a lower likelihood of working for pay among patients, and a greater proportion of reduced work hours due to AD among those who do work (Robinson et al., 2020).

Costs per patient have been estimated to increase significantly — and at a faster rate - as patients progress through AD disease stages (Robinson et al., 2020). Accordingly, effective strategies to delay the onset of severe dementia symptoms (and the subsequent care needs) are key to reducing the overall costs of AD.

Standard treatment for AD typically involves Acetylcholinesterase (AChE) inhibitors for mild and moderate AD, and Memantine for severe AD (and for patients who cannot take AChE inhibitors) (NHS, 2018). However, these medications only offer temporary symptom relief and do not halt or delay disease progression.

Recent advancements in the understanding of disease progression have led to the development of disease-modifying therapies which alter the disease's underlying biology, including gene therapies. Research finds that individuals carrying the e4 isoform of the apolipoprotein E (APOE) carry an increased risk of developing late-onset AD, whereas the e2 isoform is assumed to be neuroprotective (Serrano-Pozo, Das and Hyman, 2021; Kieu and Look, 2023). A gene therapy delivering the APOE-e2 gene into the central nervous system could potentially generate therapeutic benefits, by delaying onset or progression of AD, particularly in patients carrying only two copies of the APOE-e4 gene (Kieu and Look, 2023).

Methods

Scenarios

The primary differences between Scenarios A and B for Alzheimer's Disease are the stage at which individuals enter the model and the point at which the CGT intervention is delivered. In scenario A, the CGT is delivered at the mild AD stage, whereas in scenario B, the CGT is delivered at the mild cognitive impairment due to AD (MCI-AD) stage (Herring et al., 2021).

Population

The typical population qualified for gene therapy treatment in clinical trials is adults aged 50+, but individuals with mild dementia who are younger than 65 years are categorised as having 'early onset dementia' and likely to have other underlying characteristics (Lexeo Therapeutics, 2023). Accordingly, we assume age 65 as the starting age of the model. Two-thirds (65%) of the population with AD is estimated to be female (Alzheimer's Research UK, 2022).

The population modelled is adults aged 65 and older with mild dementia due to AD (mild AD) in scenario A or mild cognitive impairment due to AD (MCI-AD) in scenario B (see Model structure section below for further specification). MCI due to AD is a pre-dementia phase of AD, defined by noticeable memory problems or impaired judgment or decision-making, which does not affect independence of function in daily life nor meet the criteria for dementia, but has AD as a suspected etiology (Davis et al., 2018). Modelling an intervention targeting MCI due to AD would be more effective at preventing disease progression and subsequent costs (Kieu and Look, 2023). However, estimates of the MCI-AD population may be less accurate due to lack of diagnosis at that early stage (Davis et al., 2018; NICE, 2023). Accordingly, in scenario B we assume the same prevalence and incidence rate for MCI-AD as we do for mild AD, and that all AD patients are diagnosed and receive care in the predementia phase.

An estimated 982,000 people are living with dementia in the UK, with 49.7% (488,054) estimated to have mild dementia, and 37.3% and 13% estimated to have moderate and severe dementia, respectively (Carnall Farrar, 2024). We estimated an incident population of 97,316 per year, using the average number of new cases of Alzheimer's per year in England during pre-COVID years (NICE, 2023, p.202), and multiplying it by a scaling factor from (Carnall Farrar, 2024) to estimate the UK total. We use pre-COVID values, given that COVID-19 substantially affected use of NHS services (including diagnostics), and that the values were relatively stable in the 5 years before the pandemic (2013-2018). This is likely a conservative estimate given that dementia incidence is on the rise (Chen et al., 2023). We assume that newly incident cases are categorised as mild AD (or MCI-AD in the case of scenario B).

Intervention

The intervention is access to one or more hypothetical gene therapies that deliver a copy of the apolipoprotein E (APOE)-e2 gene into the central nervous system (Lexeo Therapeutics, 2023; Serrano-Pozo, Das and Hyman, 2021), in addition to SoC for management of AD symptoms (see comparator section below). Patients receive the gene therapy once on entry to the model (Kieu and Look, 2023). In the base case, we assume that the gene therapy will produce a 30% risk reduction in disease progression to the next state, based on Kieu and Look's evaluation of a hypothetical gene therapy (2023). The assumptions of a 30% risk reduction in disease progression has also been used in an economic evaluation of hypothetical disease-modifying therapies for AD, informed by recent clinical trials in AD progression, as well as a European Union consensus statement on clinically meaningful modifications in AD progression (Boustani et al., 2022). Treatment is assumed to remain effective for patients with MCI-AD, mild, and moderate AD but to

provide no benefits to patients once they are diagnosed with severe AD. We do not assume that gene therapies produce any increase in regression (or improvement) to earlier stages of disease. We also do not assume that gene therapies will produce any direct reduction in mortality risk at each disease stage, though the delays in disease progression indirectly result in deaths delayed, given the higher risk of death associated with later stages of disease (see hazard ratios in Table 46). The effect of gene therapies on disease progression is reflected in the transition matrices Table 42.

Comparator

We assume that patients in the comparator arm receive SoC only. The SoC for AD varies based on the severity of the disease, but consists of medication to manage symptoms but not to alter disease progression. For managing mild to moderate AD, the SoC involves acetylcholinesterase (AChE) inhibitors monotherapies (e.g. donepezil, galantamine and rivastigmine). Patients with severe AD or with moderate AD who are intolerant of or have a contraindication to AChE inhibitors are recommended memantine monotherapy.

Outcomes

Dementia is an irreversible progressive disease. Accordingly, outcomes are based on reductions in transition to progressive disease states (and the subsequent associated medical costs, social care costs, and other indirect costs).

Model structure

Disease progression is modelled for each scenario using a Markov model which includes the health states listed in Table 41, as shown in Figure 5. The dementia health states are categorised using CDR-SB scales (Mesterton et al., 2010; O'Bryant et al., 2008; Gustavsson et al., 2011).

Table 41 Alzheimer's disease health states and scenarios

SCENARIO A	SCENARIO B
ild AD: CDR-SB score of [4.5-9.0]	1. MCI-AD: CDR-SB score of [0.5—4.0])
2. Moderate AD: CDR-SB score of [9.5-15.5]	2. Mild AD: CDR-SB score of [4.5-9.0]
3. Severe AD: CDR-SB score of [16.0-18.0]	3. Moderate AD: CDR-SB score of [9.5-15.5]
4. Dead (absorbing state)	4. Severe AD: CDR-SB score of [16.0-18.0]
	5. Dead (absorbing state)

A similar model structure has been used previously in the economic evaluation of disease-modifying therapies for AD, as well as for non- disease-modifying therapies for AD (Davis et al., 2018; Kieu and Look, 2023; Green et al., 2019; Boustani et al., 2022).

For scenario A, all individuals are assumed to enter the model at age 65 and receive the CGT at the mild AD stage. The transition probabilities used for SoC and the gene therapies are adapted from (Potashman et al., 2021) to drop the MCI-AD state in the base case, and patients observed to transition from AD-related dementia back to MCI-AD are assumed to remain in their prior health state (Davis et al., 2018). Individuals in the mild AD state may transition to the moderate or severe AD states in the following cycles. Forward transitions to more progressive dementia states will be allowed between all disease severity states. We also allow reversal or improvement within AD dementia states to the milder health state (Davis et al., 2018).

Transition probabilities are given in Table 42 and Table 43.

Table 42 Transition probabilities for Alzheimer's disease for scenario A

STANDARD OF CARE	State	To: Mild AD	To: Moderate AD	To: Severe AD	To: Death
From	**Mild AD**	0.59	0.34	0.04	0.03
From	**Moderate AD**	0.03	0.53	0.40	0.04
From	**Severe AD**	0.00	0.02	0.89	0.10
From	**Death**	0.00	0.00	0.00	1.00

CELL AND GENE THERAPY	State	To: Mild AD	To: Moderate AD	To: Severe AD	To: Death
From	**Mild AD**	0.71	0.24	0.03	0.03
From	**Moderate AD**	0.03	0.65	0.28	0.04
From	**Severe AD**	0.00	0.02	0.89	0.10
From	**Death**	0.00	0.00	0.00	1.00

For scenario B, we include the MCI-AD state in the transition matrix as the starting point of the model. It is important to note that observed MCI-AD study populations may generate transition matrices with a higher or lower risk than the true average for the (largely unobserved) real MCI population.

Table 43 Transition probabilities for Alzheimer's disease for scenario B

STANDARD OF CARE	State	To: MCI-AD	To: Mild AD	To: Moderate AD	To: Severe AD	To: Death
From	**MCI-AD**	0.77	0.23	0.00	0.00	0
From	**Mild AD**	0.03	0.58	0.35	0.04	0
From	**Moderate AD**	0.00	0.03	0.55	0.42	0
From	**Severe AD**	0.00	0.00	0.02	0.98	0
From	**Death**	0.00	0.00	0.00	0.00	1.00

CELL AND GENE THERAPY	State	To: MCI-AD	To: Mild AD	To: Moderate AD	To: Severe AD	To: Death
From	**MCI-AD**	0.84	0.16	0.00	0.00	0
From	**Mild AD**	0.04	0.69	0.25	0.03	0
From	**Moderate AD**	0.00	0.04	0.67	0.29	0
From	**Severe AD**	0.00	0.00	0.02	0.98	0
From	**Death**	0.00	0.00	0.00	0.00	1.00

Simplifying assumptions

When modelling patients with AD we have made a few simplifying assumptions in comparison to the economic evaluations and HTA appraisals reviewed. This is to increase the generalisability of the approach, enabling the use of a generalisable model template code in R studio.

Institutionalisation

Most of the economic evaluations reviewed involve changes in care setting (i.e. a risk of moving from a community-based dementia state to a state requiring institutional care) as a distinct model state. They assume new diagnoses of AD dementia occur in a community (noninstitutional) setting (Green et al., 2019), and once patients move into institutional care, they remain there until death (Touchon et al., 2014; Whittington et al., 2022). Given that incorporating care-related states necessitates a more complex model structure which is less generalisable to other diseases, we solely consider health states, and incorporate institutionalisation in our model by attributing average healthcare, social care, and indirect costs to each health state.

Funding of health and social care

Some estimates suggest that almost 50% of social care for AD could be funded out-of-pocket. However, detailed health and social care funding data is difficult to obtain as it is not captured in a systematic way (Carnall Farrar, 2024). Given the lack of reliable data at the national level, we use a simplifying assumption that the costs of health and social care for Alzheimer's disease are realised entirely at the 'systems' level, rather than half being attributed to individuals. One advantage of this approach is that the system-level value estimates provide a fuller characterisation of health and social care costs. Nevertheless, future work should seek to more clearly disentangle to whom costs accrue in Alzheimer's disease.

Post-administration monitoring and treatment due to adverse reactions

Costs associated with post-administration monitoring and treatment due to gene therapy-related adverse reactions (e.g. immunologic events) were not addressed in our model, due to a lack of available data (Kieu and Look, 2023).

Parameter values for AD

Table 44 State parameter values for Alzheimer's disease

	PARAMETER	VALUE (CGT)	REFERENCES / NOTES
PATIENT UTILITIES	Patient utility — MCI	0.80	(Herring et al., 2021)
	Patient utility — Mild AD	0.74	(Herring et al., 2021)
	Patient utility — Moderate AD	0.59	(Herring et al., 2021)
	Patient utility — Severe AD	0.36	(Herring et al., 2021)
CAREGIVER UTILITIES	Caregiver utility — MCI	1	Assumption (Herring et al., 2021)

	Caregiver utility — Mild AD	0.964	(Herring et al., 2021) assume same caregiver disutilities across both community and institutional care settings.
	Caregiver utility — Moderate AD	0.93	(Herring et al., 2021) assume same caregiver disutilities across both community and institutional care settings.
	Caregiver utility — Severe AD	0.914	(Herring et al., 2021) assume same caregiver disutilities across both community and institutional care settings.
	Caregiver utility — Death	1	Assume no disutility
	Caregiver utility — MCI	1	Assumption (Herring et al., 2021)
	Caregiver utility — Mild AD	0.964	(Herring et al., 2021) assume same caregiver disutilities across both community and institutional care settings.
DIRECT COSTS[1]	Healthcare costs — MCI	£6,480.00	(Carnall Farrar, 2024). Costs for patients in the two years before a diagnosis is recorded.
	Healthcare costs — Mild AD	£7,766.00	(Carnall Farrar, 2024)
	Healthcare costs - Moderate AD	£7,468.00	(Carnall Farrar, 2024)
	Healthcare costs — Severe AD	£7,976.00	(Carnall Farrar, 2024)
INDIRECT COSTS[2]	Social costs — MCI	£0.00	Assumption
	Social costs — Mild AD	£16,500.00	(Carnall Farrar, 2024)
	Social costs - Moderate AD	£8,800.00	(Carnall Farrar, 2024)
	Social costs — Severe AD	£47,600.00	(Carnall Farrar, 2024)

1- Average by disease state. Includes primary care, Secondary care, Community healthcare, Mental Health, prescribing. 2- Rounded values. Include residential care, nursing care, domicilliary care, caregiver respite.

Table 45 Productivity effects for Alzheimer's disease

	PARAMETER	VALUE	REFERENCES / NOTES
GENERAL PRODUCTIVITY EFFECT PARAMETERS	Retirement age	74	Assumption, based on (Department for Work & Pensions, 2015) age band cut-off. Applies to formal employment and informal caregiving among patients.
	Average hours of work, per week	31.8	Working hours per week (ONS, 2024a)
	Average annual salary (formal employment)	£37,430	Median salary UK (ONS, 2024c)
	Average hourly wage	£18.93	Average hourly wage (ONS, 2024a)
MACRO - PATIENT	Formal employment rate, ages 65+	12.2%	(ONS, 2025). Applied to patients ages 65-74.
	Reduced productivity — MCI	20%	(Robinson et al., 2020)
	Reduced productivity — Mild AD	26%	(Robinson et al., 2020)
	Reduced productivity — Moderate AD	100%	Assumption, based on (Lin et al., 2019)
	Reduced productivity — Severe AD	100%	Assumption, based on (Lin et al., 2019)
MACRO-CARER[1]	Caregivers who have given up employment due to AD	16.1%	(Carnall Farrar, 2024).
	Caregivers employed	21.1%	(Carnall Farrar, 2024)
	Carer hours per year— MCI	828	Average per patient (Carnall Farrar, 2024)
	Carer hours per year — Mild AD	1826	Average per patient (Carnall Farrar, 2024)
	Carer hours per year — Moderate AD	3329	Average per patient (Carnall Farrar, 2024)
MESO-PATIENT[2]	Proportion of 65+ who are informal carers	8.43%	(Department for Work and Pensions, 2023). Calculated rate for ages 65-74. Assume status as informal carer if otherwise economically inactive, i.e. unemployed, retired or other.
	Average annual income for unpaid informal carers	£27,882	Assume that the value of unpaid informal care is equivalent to that of paid informal care (Park, Jit and Wu, 2018; Deloitte, 2020). Data from (ONS, 2024b), Table 20.7a Annual Gross pay - for full-time employee jobs. Use value for full-time employees, 60+, for caring, leisure and other service occupations.
	Average hours of informal caregiving per week	29.4	Weighted average from values in (ONS, 2023b)
	Reduced productivity — MCI	3.2%	Assume same as for formal employment, (Robinson et al., 2020)
	Reduced productivity — Mild AD	13.8%	Assume same as for formal employment, (Robinson et al., 2020)
	Reduced productivity — Moderate AD	100%	Assume same as for formal employment, assumed zero productivity from (Lin et al., 2019)

	Reduced productivity — Severe AD	100%	Assume same as for formal employment, assumed zero productivity from (Lin et al., 2019)
MESO-CARER	N/A		Assumption. Avoids double counting among carers.
MICRO-PATIENT	N/A		Assumes leisure time effects for patients are captured by QALYs.
MICRO-CARER[3]	Caregivers not employed	63.8%	(Carnall Farrar, 2024) Not in paid employment for other reasons (e.g. retired). Apply leisure time losses to these caregivers.
	Annual value of leisure time	£11,654	35% of the average income is used as a proxy for the monetary value of leisure time per assumptions in (Wimo et al., 2013; Johannesson et al., 1991).
	Total carer hours per year — MCI	828	Average per patient (Carnall Farrar, 2024)
	Total carer hours per year —Mild AD	1826	Average per patient (Carnall Farrar, 2024)
	Total carer hours per year — Moderate AD	3329	Average per patient (Carnall Farrar, 2024)
	Total carer hours per year — Severe AD	5728	Average per patient (Carnall Farrar, 2024)

1- Macro productivity losses are calculated for all employed caregivers and caregivers who are unemployed due to AD caregiving duties. Calculated based on an average fixed value of hours spent caregiving per AD patient weighted based on caregiver employment, rather than a percentage reduced productivity, given data availability. 2- A significant proportion of individuals aged 65+ provide informal care. The value of informal caregiving is assumed to be equivalent to that of paid labour (Park, Jit and Wu, 2018; Deloitte, 2020). 3 - Effect on leisure time activity is calculated for non-working carers. The utility values for caregivers are obtained from a study which also separately measures leisure time. Calculated based on an average fixed value of hours spent caregiving per AD patient, weighted based on caregiver employment.

Table 46 Mortality for Alzheimer's disease

	PARAMETER	VALUE	REFERENCES / NOTES
DEATH RISK	Hazard ratio — MCI	1.2	(Santabárbara et al., 2016) cited in (Martins et al., 2022)
	Hazard ratio — Mild AD	2.92	(Davis et al., 2018) cited in (Martins et al., 2022)
	Hazard ratio — Moderate AD	3.85	(Davis et al., 2018) cited in (Martins et al., 2022)
	Hazard ratio — Severe AD	9.52	(Davis et al., 2018) cited in (Martins et al., 2022)
DEATH COST[1]	End-of-life care	£8,480.62	(Wittenberg et al., 2019)

1. All costs are reported in 2024 GBP

Steady-state results for AD

Table 47 Steady-state (annual) results, Alzheimer's disease, scenario A

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£19,980,036,590	£14,722,411,947	£5,257,624,642
	Systems	-£35,031,197,104	-£35,823,584,527	£ 792,387,422
	National economy	-£29,002,782,930	-£29,958,558,885	£ 955,775,955
HEALTH OUTCOMES	QALYs	493,931	425,882	68,049 QALYs
	Life years	868,737	805,241	63,496 LYs

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care.

Table 48 Steady-state (annual) results, Alzheimer's disease, scenario B

		TREATMENT		INCREMENTAL DIFFERENCE
		CGT	SoC	
MONETISED VALUE OF OUTCOMES	Individuals	£52,047,895,865	£37,486,576,928	£14,561,318,936
	Systems	-£32,359,051,675	-£32,807,365,159	£448,313,484
	National economy	-£ 24,416,518,512	-£26,022,694,702	£1,606,176,190
HEALTH OUTCOMES	QALYs	921,327	724,089	197,236 QALYs
	Life years	1,316,247	1,107,378	208,869 LYs

Abbreviations: CGT: cell and gene therapy; QALYs: quality-adjusted life years; SoC: standard of care

Comparison of Alzheimer's results to similar evaluations

Our analysis is based on a hypothetical CGT requiring a one-off single administration of a CGT that aims to slow down and delay the progression of AD. There are currently no approved gene therapies for AD on the market. The mechanism of gene therapy can be compared to disease-modifying therapies such as aducanumab, which is administered to individuals with mild cognitive impairment or mild dementia due to AD with confirmed amyloid beta pathology. Aducanumab received accelerated approval for use in the US (FDA, 2021), but it does not have marketing authorisation in the UK or EU due to insufficient evidence on the safety, effectiveness and clinical benefit for people living with AD (EMA, 2022).

An ICER evaluation compares aducanumab administered to adults with MCI due to AD or mild AD, compared to supportive care (pharmacologic and non-pharmacologic). The analysis is conducted from the US societal perspective over a lifetime time horizon, reporting discounted outcomes using a rate of 3% (Line et al., 2021). Table 49 shows the health gains (QALYs and life-years) reported for the ICER evaluation (Line et al., 2021) comparing aducanumab to standard of care, and the results of our model comparing a hypothetical gene therapy to standard of care, run for a single patient over a lifetime (up

to age 100) and applying a 3% discount rate. A comparison of costs was not possible due to the different healthcare system contexts and cost components considered. The incremental QALY and life year gains for scenario A in our analysis are slightly higher compared to the ICER evaluation, although both analyses show improvements withing a comparable order of magnitude.

Table 49 Results of ICER evaluation vs. current analysis, lifetime

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS (3%)	INCREMENTAL GAIN DISCOUNTED LIFE YEARS (3%)
(Line et al., 2021)	US	Aducanumab versus Supportive care	0.16	0.14
Current analysis (Scenario A — mild AD)	UK	Gene therapy with SoC versus SoC only	0.43	0.47
(Line et al., 2021)	US	Aducanumab versus Supportive care	0.16	0.14
Current analysis (Scenario A — mild AD)	UK	Gene therapy with SoC versus SoC only	0.43	0.47

An economic evaluation by Kieu and Look (2023) compares a hypothetical gene therapy (along with standard of care) to standard of care alone. The analysis is conducted from the US perspective over a 20-year time horizon, reporting discounted outcomes using a rate of 3%. Table 50 shows the health gains (QALYs and life-years) reported by Kieu and Look (2023), and the results of our model run for a single patient over a 20 year time horizon and applying a 3% discount rate. A comparison of costs was not possible due to the different healthcare system contexts and cost components considered. Our analysis yields slightly lower incremental QALY and life year gains than those reported by Kieu and Look (2023), although both studies demonstrate substantial improvements in outcomes with gene therapies.

Table 50 Results of Kieu and Look (2023) vs. current analysis, 20 year time horizon

SOURCE	SETTING	INTERVENTION	INCREMENTAL GAIN DISCOUNTED QALYS	INCREMENTAL GAIN DISCOUNTED LIFE YEARS
(Kieu and Look, 2023)	US	Gene therapy with SoC versus SoC only	0.78	1.0
Current analysis (Scenario A — mild AD)	UK	Gene therapy with SoC versus SoC only	0.43	0.47

CONTRACT RESEARCH REPORT
October 2025

About us

With over 60 years of expertise, the Office of Health Economics (OHE) is the world's oldest independent health economics research organisation. Every day we work to improve health care through pioneering and innovative research, analysis, and education.

As a global thought leader and publisher in the economics of health, health care, and life sciences, we partner with Universities, Government, health systems and the pharmaceutical industry to research and respond to global health challenges.

As a government-recognised Independent Research Organisation and not-for-profit, our international reputation for the quality and independence of our research is at the forefront of all we do. OHE provides independent and pioneering resources, research and analyses in health economics, health policy and health statistics. Our work informs decision-making about health care and pharmaceutical issues at a global level.

All of our work is available for free online at **www.ohe.org.**

ohe.org

The Office of Health Economics A Company Limited by Guarantee of Registered No.09848965
OHE Consulting Ltd Registered Company No.09853113
OHE is a Charity Registration No.1170829
Registered Office 2nd Floor Goldings House, Hay's Galleria, 2 Hay's Lane, London, SE1 2HB

OHE