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DOI:
10.1007/s40273-022-01234-7

Document Version
Accepted author manuscript

Capturing the Impact of Constraints on the Cost-effectiveness of Cell and Gene Therapies: A Systematic Review

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Running head: Constraints in cost-effectiveness analyses of cell and gene therapies

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Funding Statement: This work was supported by Innovate UK [grant number 104234].

Abstract

Objective: Decision-makers need to resolve constraints on delivering cell and gene therapies to patients as these treatments move into routine care. This study aimed to investigate if, and how, constraints that affect the expected cost and health consequences of cell and gene therapies have been included in published examples of cost-effectiveness analyses (CEAs).

Method: A systematic review identified CEAs of cell and gene therapies. Studies were identified from previous systematic reviews and by searching Medline and Embase until 21-January-2022. Constraints described qualitatively were categorised by theme and summarised by a narrative synthesis. Constraints evaluated in quantitative scenario analyses were appraised by whether they changed the decision to recommend treatment.

Results: Thirty-two CEAs of cell (n=20) and gene therapies (n=12) were included. Twenty-one studies described constraints qualitatively (70% cell therapy CEAs; 58% gene therapy CEAs). Qualitative constraints were categorised by four themes: single payment models; long-term affordability; delivery by providers; manufacturing capability. Thirteen studies assessed constraints quantitatively (60% cell therapy CEAs; 8% gene therapy CEAs). Two types of constraint were assessed quantitatively across four jurisdictions (USA, Canada, Singapore, The Netherlands): alternatives to single payment models (n=9 scenario analyses); improving manufacturing (n=12 scenario analyses). The impact on decision-making was determined by whether the estimated incremental cost-effectiveness ratios crossed a relevant cost-effectiveness threshold for each jurisdiction (outcome-based payment models: n=25 threshold comparisons made, 28% decisions changed; improving manufacturing: n=24 threshold comparisons made, 4% decisions changed).

Conclusion: The net health impact of constraints is vital evidence to help decision-makers scale up the delivery of cell and gene therapies as patient volume increases and more advanced therapy medicinal products are launched. CEAs will be essential to quantify how constraints affect the cost-effectiveness of care, prioritise constraints to be resolved, and establish the value of strategies to implement cell and gene therapies by accounting for their health opportunity cost.

Key Points

1. Decision-makers across health care systems need to resolve constraints on delivering cell and gene therapies as they move into routine care settings.

2. The cost-effectiveness of cell and gene therapies can change if constraints impact the expected cost or expected health consequences of care.

3. Robust evidence from cost-effectiveness analyses will help decision-makers identify the most valuable ways to resolve capacity and organisational constraints, improve access to advanced therapies, and maximise population net health benefit.

1. Introduction

Cell and gene therapies are entering health care systems around the world [1]. These health technologies are examples of advanced therapy medicinal products (ATMPs) which typically aim to provide restorative health gains following a one-time treatment. However, constraints that impede the delivery of these treatments in routine standard care have been identified from institutional readiness programmes [2], horizon scanning of the advanced therapy pipeline [3], and the recent experience of administering cell and gene therapies in different health care systems [4]. Constraints on delivery are present across several decision-making settings, including the hospital provider, commercial manufacturer, and payer or commissioner settings [5]. These constraints reduce the relative value of care by affecting the expected health gain and/or cost of treatment per patient [6]. There are growing concerns that constraints will need to be resolved as these treatments move from the trial environment into practice, scaling the infrastructure to deliver advanced therapies in the short-term and prioritising cell and gene therapies for more prevalent diseases, and across a wider range of indications, over the longer-term [7]. Health economic evidence will be vital to help decision-makers across health care systems achieve this goal and maximise patient benefit from their limited resources.

Cell therapies, including chimeric antigen T-cell (CAR-T), tumour infiltrating lymphocyte (TIL), engineered T-cell receptor, or natural killer cell therapies, extract, modify and/or expand, and then reinfuse immune cells sourced from a patient's tumour tissue or blood [8]. Gene therapies use a vector delivery system to replace, add, or inactivate genes causative of disease in-vivo [9]. These cell and gene therapies are currently characterised by a large upfront cost and substantial uncertainty over the magnitude and duration of improvement in long-term health outcomes (life expectancy and morbidity) [10]. Cost-effectiveness analyses (CEAs) of advanced therapies are, therefore, essential to inform decision-making by providing evidence of their incremental cost and health consequences (benefit and harms) [10].

Much of the health economic literature to date has focussed on valuable solutions to the technical challenges for conducting CEAs posed by the limited evidence base for cell and gene therapies at launch. These technical challenges principally stem from the use of clinical evidence sourced from small single-armed trials, surrogate endpoints, short follow-up times relative to the proposed duration of health gains, and the use of flexible methods for survival analysis [11-17]. A complementary challenge, reported much less in the economic literature, is that the ability for cell and gene therapies to confer incremental net health benefits will

depend on whether the relevant constraints on delivery in routine care settings are resolved [10, 18].

Decision-makers across health care systems face examples of constraints repeatedly when delivering advanced therapies to patients. Health care providers will likely require investment in specialist infrastructure (such as laboratories that meet Good Manufacturing Practice standards, harmonisation between genetic testing and treatment centres, and upskilling pharmacy departments to dispense ATMPs) to treat patients in a safe and timely manner, and sufficient capacity in physical resources at the point of care (such as intensive care unit beds or leukapheresis availability) to handle patient volume [4, 19]. Similarly, commercial manufacturers may need to improve production techniques to reduce the time to treatment and minimise harm from delays for patients with severe disease activity [20]. Payers and service commissioners may require investment in data collection systems to generate evidence regarding the duration and magnitude of longer-term health benefits and harms [21], or may propose ways to manage the risk of uncertain lifetime outcomes for current and future patients by modifying the single fixed payment model for treatments [22].

In 2017, Hettle et al. [10] reported the findings from a 'mock technology appraisal' of a hypothetical cell therapy, commissioned by the National Institute for Health and Care Excellence, in preparation for the launch of these products. The report described how irrecoverable costs, including capital expenditure on equipment, new facilities, and training costs, are likely to be an important consideration when assessing the cost-effectiveness of these treatments. Similarly, Raymakers et al. [18] argued that CEAs of CAR-T therapies may need to include infrastructure and capital costs as part of the resources incurred by health care systems to deliver treatment. In the context of improving population health outcomes, the desirability of allocating limited resources for health care to reduce constraints and facilitate the delivery of cell and gene therapies can be framed as an economic question of whether the health benefit to be realised will exceed the health opportunity cost [6].

Incorporating constraints that affect the expected cost or health consequences of cell and gene therapies into CEAs can help to: (i) identify whether constraints have economic importance by their impact on the relative cost-effectiveness of care; (ii) prioritise constraints to be resolved by the extent to which they inhibit net health outcomes that are otherwise achievable; and (iii) estimate the net health benefit of alternative implementation strategies to resolve each constraint. The net health benefits of cell and gene therapies may also change over time if, for

example, average health outcomes for future incident patients improve because of learning curve effects (such as an improving ability to manage adverse events over time due to greater provider experience) [23]. Net health benefits of advanced therapies may also exhibit non-constant returns [24] as the delivery infrastructure, number of patients eligible for treatment, and types of cell and gene therapies available begin to scale. As health technology assessment organisations and health care providers are starting to gain experience with appraising the value of, and treating patients with, advanced therapies respectively, it is timely to now examine whether constraints on the delivery of these treatments have been included in CEAs. Therefore, this study aims to investigate if, and how, constraints that affect the expected cost and health consequences of cell and gene therapies have been included in published examples of CEAs.

2. Method

A systematic review was performed to identify constraints that affect the cost-effectiveness of cell or gene therapies within published examples of CEAs. The systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [25]. The review was not registered and a protocol is available from the authors on request.

A constraint was defined as "any factor that impedes or limits the amount of health status produced for a population of patients receiving specified interventions, or policies, provided by the health care system" [26]. This definition includes constraints that bind at greater patient volume due to an insufficient quantity of physical resources, and organisational constraints that are independent of patient volume but affect the expected cost and/or health consequences of care (for example, the ability to amend payment models). Constraints in any decision-making setting were included (for example, provider, manufacturer, and payer or commissioner settings). Studies were included in the review if they comprised: (i) a full CEA (health consequences expressed in natural units or quality-adjusted life years (QALYs)) of a cell or gene therapy for any disease; (ii) a decision-analytic model-based design; (iii) were published in a peer-reviewed academic journal since 2000, and (iv) were written in English. CEAs of hypothetical treatments or stem cell therapies only were excluded from the final sample.

2.1. Study Identification

Studies were identified using a two-part process. In the first part, three recent systematic reviews of economic evaluations which included advanced therapy health technologies were identified from the literature. These three reviews were by Ho et al. (dates searched: up to

November 2020) [27], Lloyd-Williams et al. (dates searched: 2000 to 2019) [28], and ten Ham et al. (dates searched: 2007 to 2019) [12]. The economic evaluations identified by these three reviews were pooled and read in full by one author (SPG) against the inclusion criteria. Studies that met the inclusion criteria were included in this review and comprised the first set of relevant CEAs published between 2000 and 2019.

In the second part of this review, a *de novo* search of the literature was undertaken to identify relevant CEAs published after 2019. This search began from 2019 to identify CEAs that were not found by the previous systematic reviews because this was the latest date searched that was common to these earlier reviews. Medline and Embase were searched electronically from 2019 until January 20th 2022 inclusive. The search strategy (reported in Supplementary Appendix 1) comprised terms for economic evaluations using the filters reported by the Centre for Reviews and Dissemination [29] and free-text terms for cell and gene therapies. The free-text terms for cell and gene therapies (brand and international non-proprietary names) were identified from the published list of advanced therapy products approved by the US Food and Drug Administration [30] and the European Medicines Agency [31] (date of list retrieval: 21 January 2022). Titles and abstracts were screened against the inclusion criteria by three authors (SPG; SJW; KP) and read in full by one author (SPG). Disagreements regarding inclusion were resolved by discussion with the same authors. The reference lists for each included study were screened to identify additional CEAs that met the inclusion criteria.

2.2. Data Extraction and Analysis

The following study design characteristics were extracted by SPG from each CEA with a standardised data extraction form and summarised in a table: author, country, disease, target population, perspective, time horizon, unit of measurement for health consequences, description of the strategies compared, and type of decision-analytic model.

Following the approach by Wright et al. [26], developed in the context of identifying constraints within economic evaluations of precision medicine test-and-treatment strategies, constraints on the delivery of cell and gene therapies that were (i) described qualitatively or were (ii) incorporated as part of the quantitative analysis were extracted from each CEA. Qualitative constraints were identified when the study described factors that would affect the uptake, scale, or implementation of the cell or gene therapy under investigation. Qualitative constraints were categorised by theme and summarised by a narrative synthesis across the sample of included studies. Quantitative constraints were identified when a CEA included a

specific input parameter or scenario analysis to represent the uptake, scale, or implementation of the cell or gene therapy under investigation. Data were extracted from sensitivity analyses to identify the impact of quantitative constraints on the magnitude of the estimated incremental cost-effectiveness ratio (ICER). To determine whether resolving these constraints changed the interpretation of the intervention's cost-effectiveness, the estimated ICERs (with and without the constraint) were compared against the relevant cost-effectiveness threshold used for that jurisdiction's health technology assessment process. The ability for decision-makers to offer uniform discounts to the list price were not considered to be a constraint for this study because of their current widespread use in health care systems [32]. This restriction did not preclude studies that modelled novel payment or data collection mechanisms.

3. Results

A flow diagram reporting how studies were identified and included is provided in Figure 1. Thirty-two CEAs of cell (n=20) [33-52] or gene therapies (n=12) [53-64] met the inclusion criteria. Table 1 summarises the design of each CEA and whether constraints that affect the cost-effectiveness of treatment were described qualitatively or included quantitatively by each study. The included studies were distributed across nine different diseases: relapsed/refractory diffuse large B-cell lymphoma (n=9) [33-40, 48]; paediatric relapsed/refractory acute lymphoblastic leukaemia (n=8) [41-48]; biallelic RPE65-mediated inherited retinal disease (n=4) [53-56]; spinal muscular atrophy type 1 (n=4) [59-62]; advanced melanoma (n=3) [50, 51, 64]; haemophilia A (n=2) [57, 58]; beta thalassemia (n=1) [63]; mantle cell lymphoma (n=1) [49]; and prostate cancer (n=1) [52]. The CEAs were designed for ten different countries: the United States (US) (n=18); The Netherlands (n=4); Japan (n=2); Singapore (n=2); Australia (n=1); Canada (n=1); Germany (n=1); Spain (n=1); Switzerland (n=1); and the United Kingdom (UK) (n=1). Twenty-one CEAs described constraints on the delivery of treatment qualitatively (which comprised 70% of CEAs for cell therapies and 58% of CEAs for gene therapies) [35-38, 40, 42, 43, 45-51, 53, 56, 59-63]. Thirteen CEAs included constraints on the delivery of treatment as a quantitative input parameter or scenario analysis (which comprised 60% of CEAs for cell therapies and 8% of CEAs for gene therapies) [33, 35, 36, 38, 40-42, 45-48, 50, 63].

<Figure 1 here>

<Table 1 here>

3.1. Qualitative Constraints

Constraints that may affect the cost-effectiveness of cell and gene therapies, which were described qualitatively by the included studies, were categorised according to four themes (subthemes in parentheses): (i) departing from a single payment model (multi-period payments; flexible pricing with more evidence; bundled reimbursement for treatment and delivery; and prospective, retrospective, short-term and long-term outcome-based payments which may vary in magnitude); (ii) long-term affordability (disease prevalence; number of indications covered; and portability between insurers); (iii) delivery by providers (initial hospital investment in physical and human capital; evolving treatment protocols over time; requirements to scale-up delivery infrastructure; and patient and health care professional preferences); and (iv) manufacturing capability (pre-treatment failure; commercial manufacturing). These four themes are now described with examples from the respective CEAs.

3.1.1. Qualitative Constraint 1: Single Payment Model

A one-time fixed payment model may constrain the delivery of advanced therapies because the risk carried by payers due to the irreversible upfront cost of treatment and uncertain long-term outcomes cannot be offset. Ten CEAs described how alternative payment models may be required for cell and gene therapies to overcome this constraint [38, 40, 43, 45-47, 56, 60, 62, 63]. Three studies explained that multi-period payments to smooth expenditure over time may reduce the short-term budget impact and improve the relative cost-effectiveness of treatment [45, 56, 62]. Lin et al. [38, 46] argued that resolving some parameter uncertainty about the magnitude and duration of treatment effectiveness over the long-term, following the collection of additional evidence, could be accounted for by a flexible pricing mechanism that makes (upward or downward) revisions to the price of treatment for future incident patients. In the context of the US health care system, two studies described how payers may try to limit the extent of hospital mark-ups which increase the total and incremental cost of providing treatment by using, for example, a fixed reimbursement that bundles payment for the treatment and provision of care [40] or by providing treatment to a pharmacy benefit manager instead of directly to the hospital [56].

Outcome-based payments that make reimbursement for treatment conditional on patients achieving specific outcomes were described by seven CEAs [38, 43, 45, 46, 56, 60, 63]. Lin et al. [38, 46] described how relevant outcomes to inform payment could be based on short-term endpoints such as remission. However, if the prior probability of achieving the short-term

endpoint is high [46] and it is a poor surrogate for longer-term outcomes, then the expected cost of treatment will be similar to that achieved by a conventional fixed payment for all patients. Alternatively, if long-term follow-up of treated patients is possible, payment could be deferred until a relevant pre-specified outcome is observed [45] or rebates on an initial payment could be granted [56]. The magnitude of any deferred payment or rebate could also vary depending on the magnitude of the observed outcome [56].

3.1.2. Qualitative Constraint 2: Long-term Affordability

Seven CEAs describe how the affordability of cell and gene therapies may constrain their delivery in the context of ensuring that decisions to allocate resources from both public and private payer budgets are sustainable [36, 38, 42, 45, 53, 56, 62]. The prevalence of disease was one driver of the concerns about affordability, such that treatments for high prevalence indications were anticipated to incur a greater budget impact than for lower prevalence indications, all else being equal [38]. Similarly, treatments licenced for multiple indications will increase the size of the population eligible for treatment and, in turn, may increase total expenditure compared with that treatment being used for a single indication [45, 56]. Zimmerman et al. [56] described a dynamic concern that the affordability of cell and gene therapies in aggregate may not be sustainable as the number of advanced therapies available to health care systems for different diseases increases in the future. A second dynamic concern about affordability in the future was raised by Uhrmann et al. [53] who explained that pricing decisions for future therapies (and their corresponding budget impact by implication) may be affected by the list price of treatments adopted by health care systems currently. For health care systems supported by private health insurance, concern about short-term affordability may be exacerbated by plan member turnover and Malone et al. [62] described how a portability mechanism may help to alleviate the challenge posed by patients who change insurance plans after receiving treatment.

3.1.3. Qualitative Constraint 3: Delivery by Providers

Constraints on delivering advanced therapies at the provider-level will limit the number of patients who can receive a cell or gene therapy. Eight CEAs described how the cost-effectiveness of these treatments may be affected by constraints on their delivery in routine settings [35, 37, 42, 48, 50, 51, 59, 61]. One key constraint was that hospitals may require investment in infrastructure to deliver cell therapy, including the need to train staff with technical skills, establishing a logistics framework to process treatment from leukapheresis to

infusion, and, potentially, access to specialist equipment such as cryopreservation and a Good Manufacturing Practice laboratory [37, 51]. The time to implement the required infrastructure may result in some patients experiencing a delay to starting their treatment [50]. The rate at which investment in infrastructure can take place may differ between hospitals within the same jurisdiction [50]. Furzer et al. [42] explain that protocols to deliver treatment may evolve over time, as health care systems gain more experience at managing a larger number of patients with these treatments, which may affect the relative effectiveness of care. Moradi-Lakeh et al. [48] also suggest that improvements in managing adverse events may increase the safety of tisagenlecleucel and reduce the cost of care. The uptake of treatment in routine settings may be affected by the preferences held by clinicians and patients [50, 59]; for example, Lindenberg et al. [50] argued that clinicians may perceive the complexity and intensity of treatment unfavourably if the impact on overall survival is not sufficiently high in magnitude and, similarly, patients may not be aware that treatment exists. Dean et al. [61] argue that the timing of gene therapy treatment is vital to identify patients who are most likely to benefit before irreversible damage occurs.

3.1.4. Qualitative Constraint 4: Manufacturing Capability

Cell therapies take time to manufacture because they are unique for each patient. Strategies to improve the production process may affect the cost-effectiveness of treatment by increasing the probability that patients achieve infusion and reducing the probability of pre-infusion mortality, adverse events, or manufacturing failure [43, 45, 49]. The cost of manufacturing autologous cell therapies at scale is higher than for conventional treatments [38] and is therefore a potential objective for future research and development to resolve over the long-term [50]. In the short-term, Lindenberg et al. [50] and Retèl et al. [51] describe how, in the context of manufacturing TIL, outsourcing production to a commercial manufacturer may help to overcome the immediate barriers to scaling production (such as limited local manufacturing facilities, regulatory knowledge, or compliance with Good Manufacturing Practice standards) but will likely increase the (total and incremental) cost of treatment.

3.2. Quantitative Constraints

Two types of constraint on the delivery of treatment were included as quantitative scenario analyses in the CEAs: the use of short-term outcome-based payments and improvements to the treatment manufacturing process. A static analysis was performed for both types of constraint which compared the estimated ICERs for a single patient cohort with and without the constraint

present [24]. These estimated ICERs are now evaluated according to a relevant threshold in the study's jurisdiction to determine whether removing the constraint changed the decisions to recommend the treatment.

3.2.1. Quantitative Constraint 1: Payment Models

Four CEAs included at least one quantitative scenario analysis that compared a uniform single payment for all patients receiving treatment with a strategy that made payment conditional on patients achieving a short-term clinical outcome (up to 12-months inclusive) [38, 42, 45, 46]. In this example, the single payment model was the constraint and the outcome-based payment models were the means to overcome this constraint. The short-term outcomes were response and remission criteria for patients who received CAR-T therapy. In these four CEAs, the price of treatment was the same under both the uniform payment for all and outcome-based payment models. Table 2 reports the estimated ICERs from nine scenario analyses (across the four CEAs) which estimated the cost-effectiveness of treatment with and without the defined short-term outcome-based payment scheme. All scenario analyses demonstrated that the respective outcome-based payment reduced the magnitude of the estimated ICER relative to a single payment for treatment. Restricting payment to patients who achieved outcomes that occurred less frequently (such as remission at 6-months and 12-months) reduced ICERs by a greater magnitude.

<Table 2 here>

Twenty-five comparisons were made against cost-effectiveness threshold values used in the respective the decision-making jurisdictions (Table 2). The decision to recommend treatment changed in seven comparisons (28% of comparisons). Eight scenario analyses were reported to inform decision-making in the USA [38, 45, 46]. The Institute for Clinical and Economic Review assumes threshold values of $50,000, $100,000, and $150,000 per QALY gained to inform their health-benefit price benchmark decisions [65]. At these threshold values, the proportion of the eight scenario analyses in which the decision to recommend treatment changed was 25% (n=2), 37.5% (n=3), and 25% (n=2) respectively. One scenario analysis was reported to inform decision-making in Canada [42]. The Canadian Agency for Drugs and Technologies in Health does not state an explicit cost-effectiveness threshold, but a value of CAD $50,000 per QALY gained is generally assumed to inform decision-making [66]. At this threshold value, the decision to recommend treatment did not change when using an outcome-based payment model.

3.2.2. Quantitative Constraint 2: Improvements to Manufacturing

The effect of improving cell therapy manufacturing processes on the relative cost-effectiveness of care was quantified by eight CEA [33, 36, 38, 40, 42, 46, 47, 50]. In this example, the performance of current manufacturing processes was the constraint, and improvements to these processes were the means to overcome this constraint. Quantitative analyses were classified as improvements to manufacturing if they adjusted the cost of producing the treatment which affected the price paid by the health care system and/or increased the number of patients who received treatment by reducing product failure or disease progression before administration. For the seven CEAs which evaluated CAR-T therapies, a decision tree structure was generally used to represent the impact of manufacturing constraints during the time between leukapheresis and infusion (such as the proportion of patients who experienced manufacturing failure, death, adverse events, or progression of disease before infusion). Patients who received an infusion then entered a second structure (including a partitioned survival analysis [36, 40, 47], Markov model [38, 46], or multi-state model [42]) to extrapolate cost and health outcomes over a longer time horizon. The cost of achieving this improved performance in manufacturing was not assessed by these seven CEAs of CAR-T therapies. For one CEA of TIL therapy, adjustments to the manufacturing process (automation and outsourcing) affected the total and incremental cost of treatment directly [50]. The cost of TIL therapy was assumed to be three-times greater if production was outsourced to a commercial manufacturer, and 30% lower if automation in production was implemented [50]. Three CEAs estimated the cost-effectiveness of CAR-T therapy when the proportion of patients who received an infusion increased, but the corresponding ICERs were not reported [35, 41, 48].

Table 3 reports the estimated ICERs from twelve scenario analyses (across the eight CEAs) that estimated the relative cost-effectiveness of cell therapies with and without constraints on manufacturing. The impact on the estimated ICERs will depend on the change in expected QALY gain and cost if a greater proportion of patients receive the cell therapy infusion (relative to the comparator strategy) and the magnitude of patients who did not receive the cell therapy in the base case analysis. The effect of reducing constraints on manufacturing had an inconsistent effect on the estimated ICERs across the sample of CEAs. Half of the scenario analyses (n=6) had a lower ICER after removing manufacturing constraints to increase the proportion of patients receiving cell therapy (Table 3). The authors of these studies did not explain why this reduction of ICERs occurred. One scenario analysis estimated no difference in the ICER after removing the manufacturing constraint to increase the proportion of patients

who received cell therapy [40]. The authors explained that this was because the the difference in cost and QALYs changed by the same proportion. In one study, the cell therapy strategy was dominant in the base case analysis and remained dominant after treatment costs were reduced due to automating production [50]. Four scenario analyses (33%) estimated a higher ICER after resolving the manufacturing constraints (Table 3). For three of these scenario analyses, increasing the proportion of patients who received cell therapy increased both incremental cost and incremental QALYs (Lin et al. [38]: Incremental cost from $360,000 to $452,000, Incremental QALYs from 2.14 to 2.70; Wang et al. [33]: Incremental cost from -S$8,477 to S$119,444, Incremental QALYs from 2.78 to 4.02; Whittington et al. [47]: Incremental cost from $329,498 to $454,900, Incremental QALYs from 7.18 to 9.10). For one scenario analysis by Lindenberg et al. [50], the outsourcing of TIL production increased cost (from –€13,620 to €57,380) whilst QALYs remained constant.

<Table 3 here>

Given that the magnitude of the estimated change in ICERs was small after resolving manufacturing constraints in these CEAs, decisions to recommend treatment were not likely to change if the base case ICER was substantially greater or lower than the relevant cost-effectiveness threshold value. Twenty-four comparisons were made against cost-effectiveness threshold values used in the respective decision-making jurisdictions (Table 3). The decision to recommend treatment changed in one comparison (4% of comparisons). Five scenario analyses reported in Table 3 informed decision-making in the USA. The decision to recommend treatment did not change by reference to the threshold values used by the Institute for Clinical and Economic Review. Three scenario analyses were reported for decision-making in Canada. The decision to recommend treatment did not change in any analysis at the assumed Canadian Agency for Drugs and Technologies in Health's cost-effectiveness threshold value (CAD $50,000 per QALY gained [66]). Two scenario analyses were reported for decision-making in Singapore. The decision to recommend treatment did not change when assuming a cost-effectiveness threshold value of one-time and three-times gross domestic product per capita [33]. Two scenario analyses were reported for decision-making in The Netherlands. The Zorginstituut Nederland uses a threshold value of €80,000 per QALY gained to inform decision-making when there is a high burden of disease [67]. At this threshold value, the decision to recommend treatment changed for one scenario analysis. In this analysis, when the cost of production increased due to outsourcing, the cost-effectiveness of TIL therapy reduced from being dominant to having an ICER of €1,138,642 per QALY gained [50].

4. Discussion

Safe and effective cell and gene therapies have the potential to improve the health status of patients substantially compared with the current standard of care. However, constraints on the delivery of treatment need to be resolved for these improvements in health status to be realised. This review found four themes described in cost-effectiveness analyses which constrain the delivery of cell and gene therapies (departing from a single payment model; long-term affordability; delivery by providers; and manufacturing capability) and two types of constraint which were evaluated in quantitative scenario analyses (payment models and improvements to manufacturing). The presence or absence of constraints can affect the expected incremental cost and QALYs of cell and gene therapies by either: (i) altering the proportion of eligible patients who receive treatment; and/or (ii) altering the cost or effectiveness of treatment directly. If health care systems are concerned with maximising population health, decision-makers will need to be aware of how relevant constraints may affect the relative cost-effectiveness of advanced therapies in their respective jurisdictions. As more cell and gene therapies are launched in the future, a greater emphasis on how health care systems can be organised to deliver these treatments cost-effectively at scale will be valuable to improve patient access and population health simultaneously.

Institutional readiness programmes designed to prepare health care systems for advanced therapies have identified that constraints on delivery may occur at different levels in the system [4]. The responsibility of resolving these disparate constraints will fall to different decision-makers. Dependencies will arise if more than one constraint (for example, ward capacity and leukapheresis capacity) must be resolved simultaneously for patients to receive treatment. Similarly, dependencies may arise between constraints that fall to different decision-makers [68]; for example, improvements to commercial manufacturing capabilities may require improvements to provider infrastructure at the same time to increase the proportion of eligible patients who receive treatment. The perspective of the economic analysis [69] will inform which constraints can be modified by the relevant decision-maker and which are assumed to be fixed in the short-run. Applying frameworks from the implementation science field [70], that help to guide the translation of health interventions into routine care settings, is one technique to identify whether dependences between constraints exist. If constraints across different perspectives are relevant to the decision problem, then reporting how cost and benefits fall across these different perspectives will likely be valuable to support decision-making [71, 72]. At a system-level, organisations such as the Advanced Therapy Treatment Centre (ATTC)

network in the UK have demonstrated a vital role in co-ordinating activities across different decision-making units to facilitate the delivery of ATMPs at scale [73]. Health care systems in different countries may benefit from investment in a similar network to start identifying potential constraints if they wish to deliver cell and gene therapies at scale in the future.

Much of the provider infrastructure to deliver cell therapy (for example, intensive care unit capacity and cryopreservation facilities) is shared between different treatments [74]. Resolving these shared infrastructure constraints could have a beneficial impact for patients across more than one indication leading to economies of scope in the production of health [75]. To investigate the economic benefit of resolving these constraints at the system-level, analyses may need to consider the impact of investing in shared infrastructure for more than one patient population. In this context, investing in shared provider infrastructure for cell therapies may be analogous with the concept of health system strengthening in the global public health literature (for example, investing in supply chains, buildings, or staff training) [76]. Hauck et al. [77] present a framework to understand how the cost-effectiveness of different interventions which use a shared platform (for example, a specialist centre to provide more than one treatment) may change across three scenarios (improving the technical efficiency of the platform; improving the capacity of the platform; and investing in a new platform). As more cell and gene therapies are launched in the future, decision-makers will need to consider how best to allocate limited resources for health care between these new treatments and the shared infrastructure to provide them, to maximise health outcomes at the population level.

The challenges raised by single payment models and long-term affordability are not unique to cell and gene therapies [78, 79]. Yet the high (total and incremental) cost of these treatments, and the forthcoming expected increase in cell and gene therapies entering health care systems, will likely keep these issues relevant to policymakers over the coming years. Outcome-based payment models in the context of cell and gene therapies improve the expected opportunity cost of care rather than benefiting observed patients receiving care directly, all else being equal. There is also a growing literature that non-marginal increases in expenditure lead to a greater health opportunity cost which can be mitigated by smoothing the time profile of costs incurred [79]. If decision-makers seek to organise services to maximise health subject to their finite budget constraint, then the value of implementing alternative payment models for cell and gene therapies should be compared against the next-best alternative (such as uniform list price discounts) and, if applicable, the added cost of data collection and administration borne by the health care system.

There is a growing health economic literature about how constraints on the delivery of care can affect health outcomes and costs to the health care system. Wright et al. [26] report a systematic review of capacity constraints in published CEAs of test-and-treatment precision medicine strategies; nine included studies quantified the impact of constraints in terms of sub-perfect implementation (for example, a proportion of eligible patients did not receive the relevant treatment due to long turn-around times for testing). Salleh et al. [80] report a systematic review of discrete event simulation studies which modelled constraints in physical resources; three included studies demonstrated how delays to treatment due to resource constraints affected patients' health (for example, treatment delays may lead symptoms of angina to worsen). The systematic review in the present study builds on this literature by demonstrating how constraints on the delivery of potentially transformative treatments, such as cell and gene therapies, may affect the expected cost and QALYs accrued by patients.

To understand the impact of resolving constraints on the cost-effectiveness of care, any change in the estimated ICERs must be compared against a relevant threshold to determine cost-effectiveness [81]. The change in ICERs alone is not sufficient to inform decision-making about whether resolving constraints on delivery is worthwhile. A change in decision-making will occur if resolving a constraint leads to a treatment which was not cost-effective becoming cost-effective, and vice versa. Expressing outcomes as incremental net (health or monetary) benefits [82] with and without the constraint present may help decision-makers to interpret its corresponding impact. Activities to resolve constraints that are presented as scenario analyses within CEAs of cell and gene therapies, such as improving the percentage of patients who receive cell therapy or the adoption of outcome-based payment models, may be cost-incurring to the health care system. Presenting such scenario analyses without incorporating the costs incurred will overestimate the expected incremental net benefit of resolving the constraint. Future CEAs should consider embedding these costs in scenario analyses, if relevant, or make their omission explicit within the reported methods.

Value of implementation analyses will likely be a useful source of evidence to quantify the net (health or monetary) benefit of reducing constraints, if these constraints limit the proportion of eligible patients who receive cell and gene therapies. Assuming that decision-makers are concerned with maximising health, value of implementation analyses can estimate the upper-bound on the cost of implementation strategies for them to be cost-effective (the expected value of perfect implementation) and the value of actual implementation strategies (by comparing the improvement in health outcomes following an implementation strategy designed to increase

the proportion of eligible patients who receive treatment with its corresponding cost) [6]. The framework for value of implementation analyses by Fenwick et al. [6] has since been developed to include subgroup analyses [83], the natural diffusion of health technologies without implementation strategies for future incident patients [84], and non-constant incremental cost and QALYs as implementation increases over time [24]. Quantifying the value of implementation strategies for cell and gene therapies will provide relevant information for decision-makers to help inform practical decisions about how to allocate resources to facilitate the delivery of ATMPs at scale in the future.

One limitation of this study was that the review excluded CEAs in the grey literature to inform health technology assessment. However, the sample of published CEA was sufficient to identify relevant examples of constraints across studies designed for different decision-making jurisdictions. Using previous systematic reviews to identify CEAs of cell and gene therapies may also be a limitation of this study if these published systematic reviews inadvertently omitted a relevant study from their sample. To mitigate this risk, more than one systematic review (with overlapping inclusion criteria and search dates) was used to identify relevant published CEAs. Finally, there is a broader literature that describes alternative payment models and constraints on delivery for cell and gene therapies [4, 85]. Whilst this systematic review focussed on examples within cost-effectiveness analyses only, this broader literature can be useful for decision-makers to understand the extent of barriers and facilitators known to date.

Future research could undertake a content analysis [86] of the deliberations and decisions in the public domain made by health technology assessment agencies around the world to explore if, and how, constraints which may affect the cost-effectiveness of cell and gene therapies have been addressed to date. Identifying a consensus view about potential constraints on delivery which may affect the cost-effectiveness of current and forthcoming cell and gene therapies can be identified by undertaking a Delphi process with relevant stakeholders across the health care system (for example, national decision-makers, service commissioners, regional providers, commercial manufacturers, health care professionals who are central to the delivery of these treatments including specialist pharmacists and nurses with expertise in ATMPs, and current or future patients) [87]. Future research could also perform a static or dynamic value of implementation analysis [24] to quantify the value of different strategies to scale up the delivery of specific cell and gene therapies for prevalent and incident patient cohorts.

5. Conclusion

Decision-makers will need to consider how best to resolve constraints on the delivery of cell and gene therapies, to scale the provision of these treatments and deliver their anticipated health benefits to patients, as the demand for ATMPs increases in the future. Coordination between different decision-making units and horizon scanning to anticipate future treatments and patient volume will be essential to identify potential constraints and strategies to overcome them. Health economic evidence, and CEA specifically, can inform decision-making by quantifying the impact of constraints on the cost-effectiveness of care, helping to prioritise constraints to be resolved, and estimating the value of strategies to implement cell and gene therapies across health care systems. By considering the health economic impact of resolving constraints though investment decisions or by reorganising service delivery, decision-makers can ensure that resources are allocated to improve the health of patients who receive cell and gene therapies whilst simultaneously accounting for the opportunity cost of these decisions.

Statements and Declarations

Declarations: Sean P. Gavan and Katherine Payne declare that they have no conflict of interest. Stuart J. Wright reports consultancy fees for acting on a steering group for a project investigating the impact of including supply constraints in economic evaluations for PHMR on a project funded by Roche. Fiona Thistlethwaite reports institutional research grant income from Instil Bio; honoraria from GSK, Bristol Myers Squibb, Janssen, and Pfizer; advisory committee membership for Immatics; speaker fees from Kite/Gilead; is principal investigator for commercial ATMP trials (Adaptimmune, GSK, T-knife Therapeutics, Instil Bio) but does not receive personal payment; and is director of iMATCH (Innovate Manchester Advanced Therapy Centre Hub) supported by Innovate UK.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sean P. Gavan, Stuart J. Wright, and Katherine Payne. The first draft of the manuscript was written by Sean P. Gavan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding: This work was supported by Innovate UK [grant number 104234]. For the purpose of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising.

Data Availability: All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Table 1. Summary of Included Cost-effectiveness Analyses (n=32)

							Constraints Included	
Author (Year)	**Country**	**Disease**	**Treatment**	**Perspective**	**Time Horizon**	**Model Type**	**Qualitative**	**Quantitative**
Cell Therapy								
Wang et al. (2021) [33]	Singapore	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah®)	Private insurance payers	Lifetime	Decision tree and partitioned survival analysis	No	Yes
Qi et al (2021) [34]	USA	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah®)	Third-party payer	Lifetime	Response-based partitioned survival analysis	No	No
Wakase et al. (2021) [35]	Japan	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah®)	Public healthcare payer	Lifetime	Decision tree and partitioned survival analysis	Yes	Yes
Cher et al. (2020) [36]	Singapore	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah®)	Health care system	15-years	Decision tree and partitioned survival analysis	Yes	Yes
Liu et al. (2021) [37]	USA	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah®); Axicabtagene ciloleucel (Yescarta®)	US Payer	Lifetime	Partitioned survival analysis	Yes	No
Lin et al. (2019) [38]	USA	Relapsed/refractory diffuse large B-cell lymphoma	Tisagenlecleucel (Kymriah); Axicabtagene ciloleucel (Yescarta®)	Health care payer	Lifetime	Markov model	Yes	Yes
Whittington et al. (2019) [39]	USA	Relapsed/refractory diffuse large B-cell lymphoma	Axicabtagene ciloleucel (Yescarta®)	Public payer; Commercial payer	24-months; Lifetime	Decision tree and semi-Markov partitioned survival analysis	No	No

Roth et al. (2018) [40]	USA	Relapsed/refractory diffuse large B-cell lymphoma	Axicabtagene ciloleucel (Yescarta®)	US payer	Lifetime	Decision tree and partitioned survival analysis	Yes	Yes
Wakase et al. (2021) [41]	Japan	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	Public healthcare payer	Lifetime	Decision tree and partitioned survival analysis	No	Yes
Furzer et al. (2020) [42]	Canada	Paediatric acute lymphoblastic leukaemia at second relapse	Tisagenlecleucel (Kymriah®)	Public insurer	Lifetime	Multi-state microsimulation	Yes	Yes
Santasusana et al. (2020) [43]	Spain	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	Spanish NHS	Lifetime	Partitioned survival analysis	Yes	No
Thielen et al. (2020) [44]	The Netherlands	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	Societal; Health care system	Lifetime	Partitioned survival analysis	No	No
Sarkar et al. (2019) [45]	USA	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	Third-party payer; Societal	Lifetime	Individual-based state-transition microsimulation	Yes	Yes
Lin et al. (2018) [46]	USA	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	US health care payer	Lifetime	Markov model	Yes	Yes
Whittington et al. (2018) [47]	USA	Relapsed/refractory paediatric acute lymphoblastic leukaemia	Tisagenlecleucel (Kymriah®)	Payer	Lifetime	Decision tree and semi-Markov partitioned survival analysis	Yes	Yes
Moradi-Lakeh et al. (2021) [48]	Switzerland	Relapsed/refractory paediatric acute lymphoblastic	Tisagenlecleucel (Kymriah®)	Health care system; societal	Lifetime	Partitioned survival analysis	Yes	Yes

		leukaemia and relapsed/refractory diffuse large B-cell lymphoma						
Simons et al. (2021) [49]	USA	Relapsed/refractory mantle cell lymphoma	Brexucabtagene autoleucel (Tecartus™)	USA payer	Lifetime	Partitioned survival analysis	Yes	No
Lindenberg et al. (2020) [50]	The Netherlands	Advanced melanoma	TIL	Dutch health care system	10-years	Markov model	Yes	Yes
Retèl et al. (2018) [51]	The Netherlands	Advanced melanoma	TIL	Dutch health care system	10-years	Markov model	Yes	No
Gong et al. (2014) [52]	USA	Asymptomatic pre-docetaxel metastatic castration-resistant prostate cancer	Sipuleucel-T (Provenge®)	Societal	Lifetime	Markov model	No	No
Gene Therapy								
Uhrmann et al. (2020) [53]	Germany	Biallelic RPE65-mediated inherited retinal disease	Voretigene neparvovec (Luxturna)	Societal	Lifetime	Individual sampling model	Yes	No
Viriato et al. (2020) [54]	UK	Biallelic RPE65-mediated inherited retinal disease	Voretigene neparvovec (Luxturna®)	National Health Service and Personal Social Services	Lifetime	Markov state transition model	No	No
Johnson et al. (2019) [55]	USA	Biallelic RPE65-mediated inherited retinal disease	Voretigene neparvovec (Luxturna®)	Not reported	Lifetime	Cohort state transition model	No	No
Zimmerman et al. (2019) [56]	USA	Biallelic RPE65-mediated inherited retinal disease	Voretigene neparvovec (Luxturna®)	Health care system & societal	Lifetime	Markov model	Yes	No
Cook et al. (2020) [57]	USA	Haemophilia A	Valoctocgene roxaparvovc (Roctavian™)	Health care system	Lifetime	Individual-based state transition microsimulation	No	No

Machin et al. (2018) [58]	USA	Haemophilia A	Experimental AAV gene therapy	Third-party payer	10-years	Cohort state-transition Markov model	No	No
Shih et al. (2021) [59]	Australia	Spinal muscular atrophy type 1	Newborn screening plus onasemnogene abeparvovec (Zolgensma®)	Societal	60-years	Markov model	Yes	No
Broekhoff et al. (2021) [60]	The Netherlands	Spinal muscular atrophy type 1	Onasemnogene abeparvovec (Zolgensma®)	Societal	Lifetime	Microsimulation	Yes	No
Dean et al. (2021) [61]	USA	Spinal muscular atrophy type 1	Onasemnogene abeparvovec (Zolgensma®)	Commercial payer	Lifetime	Markov model	Yes	No
Malone et al. (2019) [62]	USA	Spinal muscular atrophy type 1	Onasemnogene abeparvovec (Zolgensma®)	Commercial payer	Lifetime	Markov model	Yes	No
Kansal et al. (2021) [63]	USA	Transfusion-dependent Beta thalassemia	Betibeglogene autotemcel (Zynteglo™)	US commercial payer	Lifetime	Discretely integrated condition event	Yes	Yes
Almutairi et al. (2019) [64]	USA	Malignant unresectable melanoma (stage IIIb to IVM1c)	Talimogene laherparepvec (Imlygic®)	Public and private payers	Lifetime	State transition Markov model	No	No

Abbreviations: NHS, National Health Service; TIL, Tumour infiltrating lymphocyte; UK, United Kingdom; USA, United States of America. Constraints Included reports whether constraints were included qualitatively or as part of quantitative analyses.

Table 2. Quantitative Scenario Analyses: Short-term Outcome-based Payments

Lead Author	Intervention	Comparator	Payment Rule	ICER without Payment Rule	ICER with Payment rule	Decision Change
Lin [38]	Tisagenlecleucel (Kymriah®)	Salvage chemoimmunotherapy & stem cell transplantation	Payment for CAR-T only if complete response achieved	$168,000 per QALY gained	$88,300 per QALY gained	$50,000: No $100,000: Yes $150,000: Yes
Lin [38]	Axicabtagene ciloleucel (Yescarta®)	Salvage chemoimmunotherapy & stem cell transplantation	Payment for CAR-T only if complete response achieved	$129,000 per QALY gained	$90,500 per QALY gained	$50,000: No $100,000: Yes $150,000: No
Lin [38]	Tisagenlecleucel (Kymriah®)	Salvage chemoimmunotherapy & stem cell transplantation	Payment for CAR-T only if 90-day complete or good partial response is achieved	$168,000 per QALY gained	$126,000 per QALY gained	$50,000: No $100,000: No $150,000: Yes
Lin [38]	Axicabtagene ciloleucel (Yescarta®)	Salvage chemoimmunotherapy & stem cell transplantation	Payment for CAR-T only if 90-day complete or good partial response is achieved	$129,000 per QALY gained	$89,300 per QALY gained	$50,000: No $100,000: Yes $150,000: No
Furzer [42]	Tisagenlecleucel (Kymriah®)	Standard care including chemotherapy and stem cell transplantation	Payment for CAR-T only if remission is achieved	CAD $ 170,000 per QALY gained	CAD $141,000 per QALY gained	CAD $50,000: No
Sarkar [12]	Tisagenlecleucel (Kymriah®)	Standard of care chemotherapy and stem cell transplantation	Payment for CAR-T only if response is achieved	$75,600 per QALY gained	$64,600 per QALY gained	$50,000: No $100,000: No $150,000: No
Lin [46]	Tisagenlecleucel (Kymriah®)	Blinatumomab	Payment for CAR-T only if patient achieves initial remission	$74,000 per QALY gained	$61,000 per QALY gained	$50,000: No $100,000: No $150,000: No
Lin [46]	Tisagenlecleucel (Kymriah®)	Blinatumomab	Payment for CAR-T if in remission at 6-months	$74,000 per QALY gained	$47,000 per QALY gained	$50,000: Yes $100,000: No $150,000: No
Lin [46]	Tisagenlecleucel (Kymriah®)	Blinatumomab	Payment for CAR-T if in remission at 12-months	$74,000 per QALY gained	$28,000 per QALY gained	$50,000: Yes $100,000: No $150,000: No

Abbreviations: CAD, Canadian dollar; CAR-T, Chimeric antigen receptor T-cell; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year. ICER without payment rule corresponds with paying list price for all patients. Decision Change illustrates whether the decision to recommend treatment changes at different cost-effectiveness threshold values (expressed in monetary units per QALY gained). Values for Lin et al. [38] assume a 5-year progression-free survival of 35% for tisagenlecleucel and 40% for axicabtagene ciloleucel. Values for Lin et al. [46] assume a 5-year relapse-free survival of 40% for tisagenlecleucel.

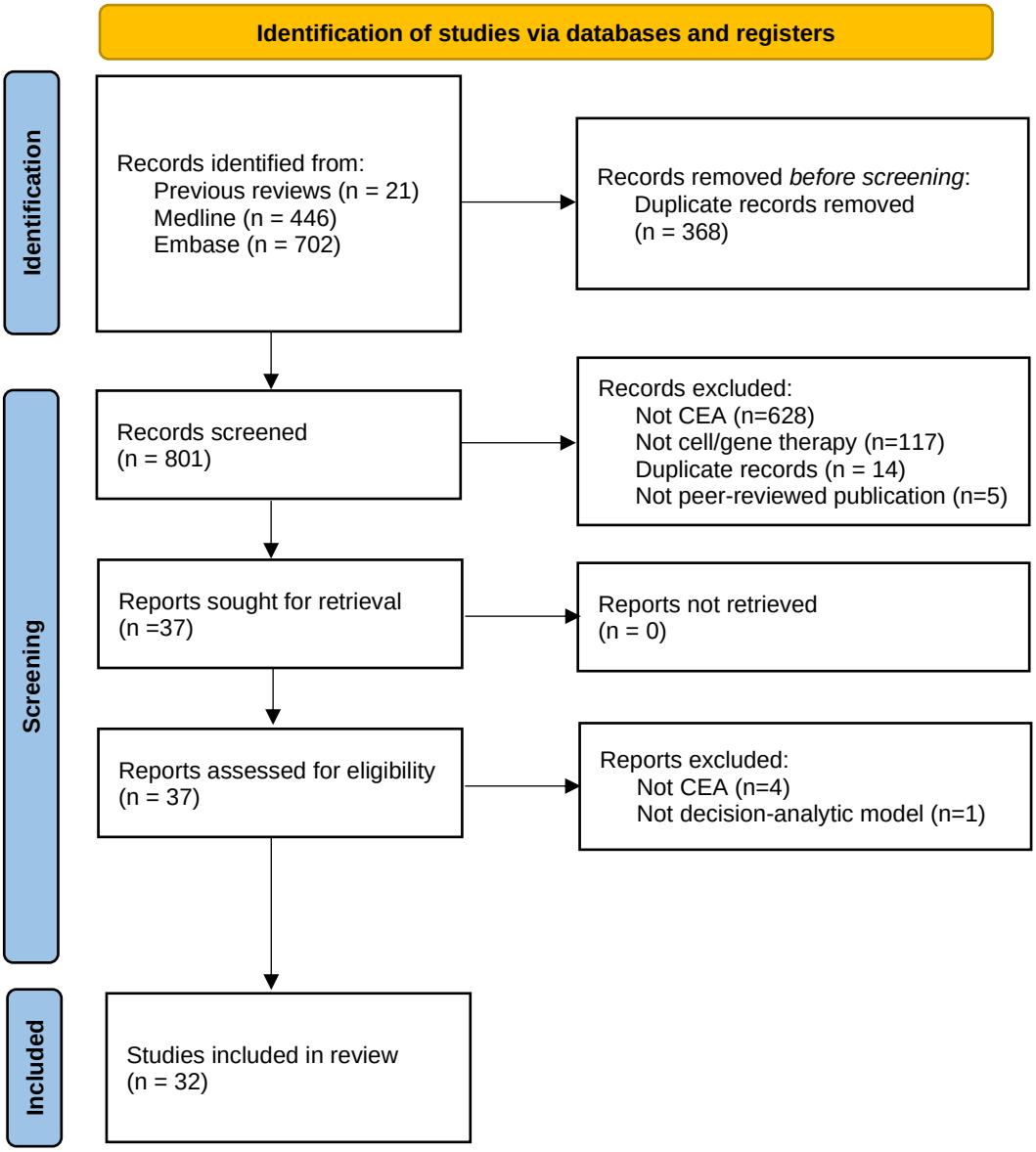
Table 3. Quantitative Scenario Analyses: Improving Cell Therapy Manufacturing

Lead Author	Intervention	Comparator	Constraint	ICER With Constraint	ICER Without constraint	Decision Change
Cher [36]	Tisagenlecleucel (Kymriah®)	Salvage chemotherapy	23% of patients did not receive CAR-T due to disease progression or manufacturing failure	S $686,516 per QALY gained	S $536,204 per QALY gained	S $88,991: No S $266,973: No
Lin [38]	Tisagenlecleucel (Kymriah®)	Salvage chemoimmunotherapy & stem cell transplantation	29.5% of patients did not receive CAR-T due to severe adverse events, manufacturing failure, or death	$168,000 per QALY gained	$167,000 per QALY gained	$50,000: No $100,000: No $150,000: No
Lin [38]	Axicabtagene ciloleucel (Yescarta®)	Salvage chemoimmunotherapy & stem cell transplantation	6.9% of patients did not receive CAR-T due to severe adverse events, manufacturing failure, or death	$129,000 per QALY gained	$131,000 per QALY gained	$50,000: No $100,000: No $150,000: No
Roth [40]	Axicabtagene ciloleucel (Yescarta®)	Salvage chemotherapy	9% of patients did not receive CAR-T due to adverse events, progression of disease, or unsuccessful manufacturing	$58,146 per QALY gained	$58,146 per QALY gained	$50,000: No $100,000: No $150,000: No
Furzer [42]	Tisagenlecleucel (Kymriah®)	Standard care including chemotherapy and stem cell transplantation	11% of patients did not receive CAR-T due to manufacturing failure	CAD $141,000 per QALY gained	CAD $139,000 per QALY gained	CAD $50,000: No
Furzer [42]	Tisagenlecleucel (Kymriah®)	Standard care including chemotherapy and stem cell transplantation	8% of patients did not receive CAR-T due to death before infusion	CAD $141,000 per QALY gained	CAD $134,000 per QALY gained	CAD $50,000: No
Furzer [42]	Tisagenlecleucel (Kymriah®)	Standard care including chemotherapy and stem cell transplantation	18% of patients did not receive CAR-T due to manufacturing failure or death before infusion	CAD $141,000 per QALY gained	CAD $132,000 per QALY gained	CAD $50,000: No
Lin [46]	Tisagenlecleucel (Kymriah®)	Blinatumomab	19% of patients did not receive CAR-T due to manufacturing failure or death before infusion	$61,000 per QALY gained	$60,000 per QALY gained	$50,000: No $100,000: No $150,000: No
Whittington [47]	Tisagenlecleucel (Kymriah®)	Clofarabine	Proportion of patients (value not reported) did not receive CAR-T infusion	$45,871 per QALY gained	$50,000 per QALY gained	$50,000: No $100,000: No $150,000: No

Wang [33]	Tisagenlecleucel (Kymriah®)	Salvage chemotherapy	31% did not receive CAR-T before infusion	Dominant	S $29,712*	S $88,991: No S $266,973: No
Lindenberg [50]	TIL	Ipilimumab	Cost of TIL production impacted by lack of automation	Dominant	Dominant	€80,000: No
Lindenberg [50]	TIL	Ipilimumab	Cost of TIL production impacted by lack of outsourcing	Dominant	€1,138,642 per QALY gained	€80,000: Yes

Abbreviations: CAR-T, Chimeric antigen receptor T-cell; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year. S $, Singapore dollar; TIL, Tumour infiltrating lymphocyte. ICER without constraint corresponds with removal of the constraint for all patients. Decision change illustrates whether the decision to recommend treatment changes at different cost-effectiveness threshold values (expressed in monetary units per QALY gained). *Calculated manually from reported incremental cost and incremental QALY values. Values for Lin et al. [38] assume a 5-year progression-free survival of 35% for tisagenlecleucel and 40% for axicabtagene ciloleucel. Values for Lin et al. [46] assume a 5-year relapse-free survival of 40% for tisagenlecleucel.

Figure 1. PRISMA Diagram of Included Studies



Electronic Supplementary Material

Capturing the Impact of Constraints on the Cost-effectiveness of Cell and Gene Therapies: A Systematic Review

PharmacoEconomics

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Online Supplementary Material: Medline Electronic Database Search Strategy

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2 exp "costs and cost analysis"/
3 Economics, Dental/
4 exp economics, hospital/
5 Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
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Online Supplementary Material: Embase Electronic Database Search Strategy

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