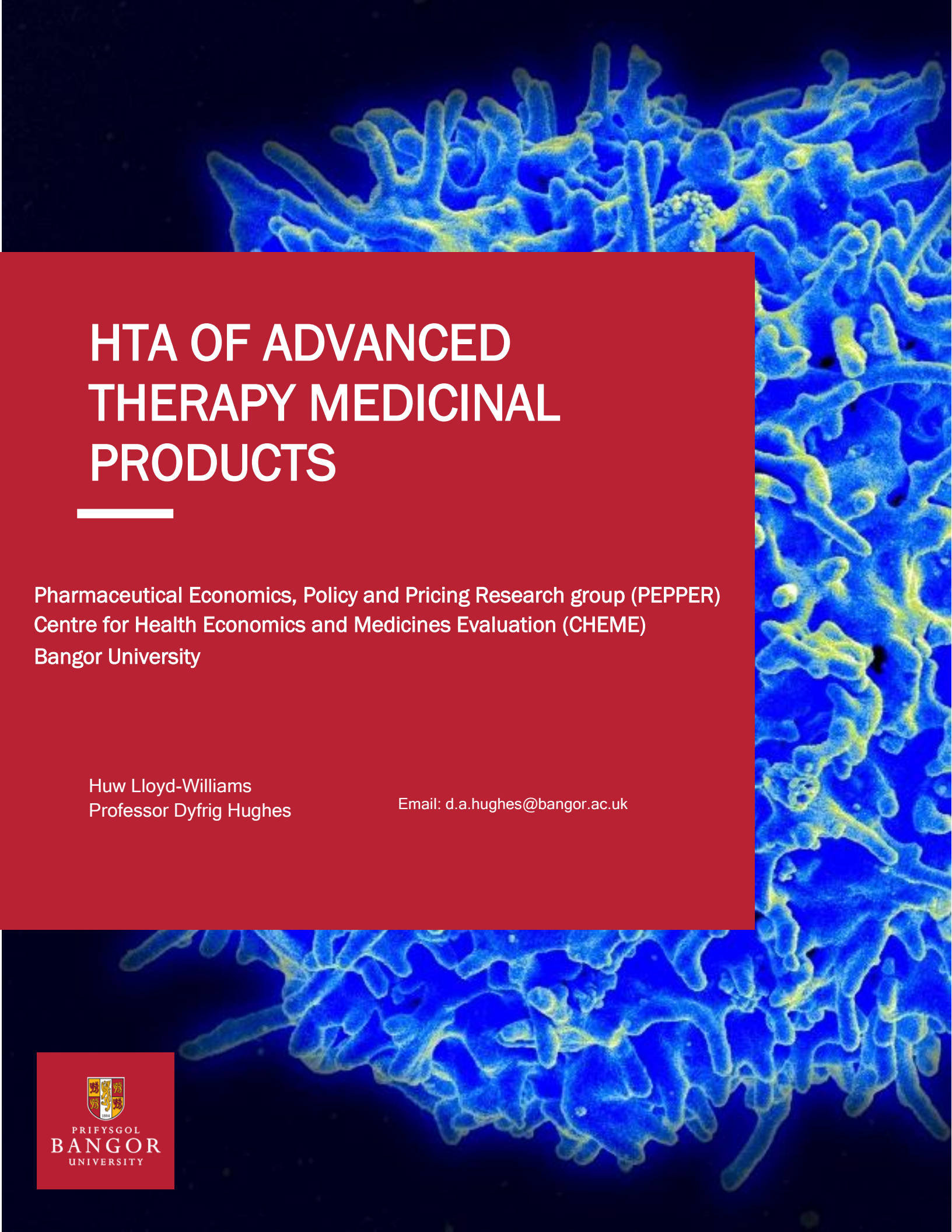

HTA OF ADVANCED THERAPY MEDICINAL PRODUCTS

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Conflict of Interest:

HLI-W and DAH declare that they have no conflict of interest.

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EXECUTIVE SUMMARY

Advanced Therapy Medicinal Products (ATMPs) pose specific challenges in evidence generation, health technology assessment (HTA) and financing. A key feature of ATMPs is their price, which for some, can exceed £1m per patient. Such high up-front costs make ATMPs particularly problematic in terms of affordability for healthcare payers, especially as the usual thresholds of cost-effectiveness applied in the appraisal of conventional health technologies, are unlikely to be met. Moreover, there may be methodological challenges, such as in relation to uncertainty in the evidence of the effectiveness of newly approved ATMPs; the nature of the distribution of costs in relation to the accrual of benefits, and how these are affected by choice of discount rates; whether curative treatments may be considered differently to treatments that create smaller incremental benefits; and consideration of value attributes that may not be captured adequately in the quality-adjusted life year (QALY).

This report provides a state-of-the-art perspective on key methodological issues relating to the economic evaluation and health technology appraisal of ATMPs. It sets out key recommendations for the future assessment and appraisal of ATMPs.

- Advanced Therapy Medicinal Products (ATMPs) which include gene and somatic-cell therapies and tissue-engineered medicines, have the potential to transform current care pathways by offering durable and potentially curative outcomes.
- There are currently 10 ATMPs available within the European Union. There are over 959 companies worldwide developing ATMPs, with products being tested in 1052 clinical trials. As many as 70 ATMPs could become available in the UK by 2024, although not all will progress to gaining marketing authorisation.
- The global ATMP market is estimated to reach £9bn to £14bn by 2025.
- Some ATMPs are exceptionally expensive. Tisagenlecleucel has a UK list price of £282,000 for a one-time infusion, Strimvelis® costs £594,000 per patient, and autologous CD34+ cells encoding βA-T87Q-globin gene (Zynteglo®) for beta thalassaemia costs over £1m. The manufacturers of onasemnogene abeparvovec-xioi (Zolgensma®) for spinal muscular atrophy will offer a global managed-access programme, but has a current US price of $2.1m.
- Healthcare providers are faced with difficult decisions concerning their value for money, reimbursement and budget impact implications.

- The first wave of ATMPs assessed by the National Institute for Health and Care Excellence (NICE) were recommended for use via the cancer drugs fund (in England). ATMPs qualifying as life-extending end-of-life treatments are appraised according to a higher cost effectiveness threshold of £50,000 per quality-adjusted life year (QALY). It is anticipated that some ATMPs with non-cancer indications may be evaluated via the NICE Highly Specialised Technologies route in future, which operates a threshold of up to £300,000 per QALY.
- Economic evaluations of ATMPs conducted to date suggest that their incremental cost effectiveness ratios are generally high and associated with significant uncertainty and potential bias owing to methodological challenges caused by the paucity of data on long-term outcomes.
- Often, HTA bodies have only phase I and II studies to assess the clinical effectiveness of ATMPs, and most studies are multicentre, open-label and lack comparator data. In the absence of trial-based comparisons, there is increased reliance on indirect comparisons using historical controls, which introduces significant bias. Additional challenges in assessing the clinical effectiveness of ATMPs are the lack of long-term outcome data, including health-related quality of life and survival, and reliance on endpoints that may not be good surrogates for outcomes that matter to patients.
- Some consider unique features of ATMPs to warrant a high cost-effectiveness threshold. These features include: the potentially curative nature of the therapies along with lifetime benefits; the changing nature of the product characteristics over time; potential long-term safety issues; organisational and scaling issues; and the significant up-front cost that face payers. However, whether these features are unique to ATMPs is debatable – many surgical interventions have high up-front costs with lasting benefits; antimicrobial treatments are curative; and several (small molecule and biologic) medicines have potential long-term safety concerns.
- The differential timing in the costs and accrual of benefits associated with ATMPs suggests that time preference, and the choice of discount rate, is likely to be more impactful on their cost-effectiveness compared to many other conventional health technologies. The application of the standard 3.5% per annum discount rate for benefits, for instance, will reduce the net present value of the long-term effects of ATMPs and increase their incremental cost-effectiveness ratio. However, NICE already applies a lower discount rate (1.5% per annum) for costs and benefits relating to treatments that restore people to full or near-full health when they would otherwise die.
- Current methods of economic evaluation are likely to be sufficient for analysing ATMPs; and the exiting methods of health technology appraisal, as applied across the UK, are appropriate for NHS decision-making.

RECOMMENDATIONS

- Clinical trial evidence for ATMPs is generally of low quality, which is likely a function of the rarity of the diseases treated and the regulatory context for demonstrating efficacy. For health technology assessment, consideration of comparative clinical effectiveness is necessary, and further evidence, including from post-approval studies should be generated to reduce uncertainty in key clinical parameters.
- Evidence on comparative clinical effectiveness should ideally come from well-designed pragmatic trials that minimise bias through randomisation, and measure health outcomes that are relevant to patients. The use of observational data places a high risk of bias which cannot be fully mitigated through adjustment for confounding factors. Application of methods such as network meta-analyses may assist in estimating relative treatment effects, but are also subject to potential biases from indirect treatment comparison.
- There is a lack of data on disease progression and long term effects which undermine the accuracy of economic model projections. Assessment of lifetime costs and consequences is essential to avoid time horizon bias in economic analyses but, because of the paucity of data from clinical studies, transition probabilities are often not calculable for parameterising economic models. Modelled extrapolations should therefore consider different parametric functions for survival, different assumptions of treatment benefit (such as proportional versus other hazard functions), different probabilities if based on responder analysis, and different scenarios for durability of treatment effect.
- Data on health-related quality of life and health state utilities should be captured in all clinical studies of ATMPs, and measured in routine practice. The lack of data on health outcomes to estimate QALYs in existing economic evaluations of ATMPs could be addressed by administering the EQ-5D-5L to all patients prescribed ATMPs.
- Economic modelling assumptions about the efficacy, comparative effectiveness, resource use, health utilities, long term costs and outcomes of ATMPs should be tested extensively using relevant scenario and sensitivity analyses, including consideration of structural in addition to parameter uncertainty. Scenarios of treatment benefit must consider conservative estimates as well as optimistic claims of cure, and based upon the intention to treat population. Impacts of adverse drug reactions need to be considered, as well as associated treatments prescribed to mitigate their effects.
- Current ATMPs are purchased via standard methods of reimbursement with an upfront cost for the product irrespective of success or failure of the treatment. Innovative payment methods need to be developed to manage and share risk to facilitate timely patient access while the evidence matures. Whilst a simple patient access scheme discount has been negotiated for all the NICE-approved

ATMPs so far, it may be necessary or desirable to look at different ways of paying. Upfront payments provides reimbursement to the manufacturers of the full value of the ATMP, with all the financial risks placed on the NHS. Alternatives, such as annual payments over a defined period dependent on continued successful response to treatment, and outcomes-based contracting payment schemes are likely to feature in the near-future commissioning of ATMPs.

- An important policy decision concerns whether there are equity considerations and/or specific features of ATMPs, which make them distinct from other health technologies to merit greater flexibility around the cost-effectiveness threshold, beyond that which currently exists. It is conceivable that there may be features associated with ATMPs or the diseases they treat which may be valued higher by society than the health which is displaced as the opportunity cost of their approval. To address this issue, evidence is needed on societal preferences in support (or otherwise) of the value of the benefits of ATMPs compared with other health technologies.

A Systematic Review of Economic Evaluations of Advanced Therapy Medicinal Products

Summary

BACKGROUND Advanced Therapy Medicinal Products (ATMPs) represent a new category of medicinal products with a potential for transformative improvements in health outcomes but at exceptionally high prices. Routine adoption of ATMPs requires robust evidence of their cost-effectiveness.

METHODS A systematic literature review of economic evaluations of ATMPs, including gene therapies, somatic cell therapies, and tissue-engineered products, was conducted. Literature was searched using MedLine, Embase, PubMed, Cochrane Register, the NHS Economic Evaluation Database and the grey literature of HTA organisations with search terms relating to ATMPs and economic evaluations. Titles were screened independently by two reviewers. Articles deemed to meet the inclusion criteria were screened independently on abstract, and full texts reviewed. Study findings were appraised critically.

RESULTS 4,514 articles were identified, of which 23 met the inclusion criteria. There was some evidence supporting the cost-effectiveness of: CAR T-cell therapy axicabtagene ciloleucel (Yescarta®), embryonic neural stem cells, tumour infiltrating lymphocytes, in vitro expanded myoblast, autologous chondrocyte implantation, ex vivo gene therapy (Strimvelis®) and voretigene neparvovec (Luxturna®). However, estimates of cost-effectiveness were associated with significant uncertainty and high likelihood of bias, resulting from largely unknown long-term outcomes, a paucity of evidence on health state utilities, and extensive modelling assumptions.

CONCLUSIONS There are critical limitations to the economic evidence for ATMPs, most notably in relation to evidence on the durability of treatment effect, and the reliability of opinion-based assumptions necessary when evidence is absent.

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs), which include gene therapies, somatic cell therapies, and tissue-engineered products have the potential for transformative improvements in health outcomes for a wide range of diseases, including certain cancers, neurodegenerative and cardiovascular diseases [1,2]. Clinical application of somatic cell therapies and tissue-engineered products is frequently referred to as 'regenerative medicine'. The number of ATMPs being approved is rising [3] and given their high cost, there is a pressing need for robust economic evidence of these therapies in order to inform decisions made by healthcare payers.

ATMPs pose specific challenges in evidence generation, health technology assessment (HTA) and financing [4]. A key feature of ATMPs is their price, which can in some instances exceed £1m per patient. Such high (often up-front) costs make ATMPs particularly problematic in terms of meeting usual thresholds of cost-effectiveness and being affordable to healthcare payers. Moreover, there may be methodological challenges, such as in relation to uncertainty in the evidence of the effectiveness of newly approved ATMPs; the nature of the distribution of costs in relation to the accrual of benefits, and how these are affected by choice of discount rates; whether curative treatments may be considered differently to treatments that create smaller incremental benefits; and consideration of value attributes that may not be captured adequately in the quality-adjusted life year (QALY).

The National Institute for Health and Care Excellence (NICE) in the UK suggested that a completely new reference case is not needed. Their mock economic evaluation of a CAR (chimeric antigen receptor) T-cell therapy accepted existing methods of economic evaluation as being 'fit for purpose' in the evaluation of ATMPs [5]. More recently, the independent US-based Institute for Clinical and Economic Review following a review in collaboration with NICE and the Canadian Agency for Drugs and Technologies in Health, published adaptations to its value assessment framework for potential cures and other treatments that qualify as high-impact "single or short-term therapies" [6]. Marsden et al (2019) [7] suggested new analytic approaches are required, suggesting that "patients with rare genetic diseases, along with the gene replacement therapies they use, present a unique set of conditions that warrant equally unique analytic approaches to estimating value for money." Similarly, Drummond et al (2019) [8] suggested that some unique characteristics need to be taken into account.

The aim of this study was to review and critique published economic evaluations of ATMPs, in order to: (i) highlight current evidence on the cost-effectiveness of ATMPs; (ii) identify specific methodological challenges; and (iii) assess how these challenges were approached by analysts.

METHODS

Protocol, registration and reporting

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, reference CRD42019125069). The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9].

Review question

The principal review question was: What are the main challenges and solutions for the economic evaluation of advanced therapy medicinal products (ATMPs)?

Search strategy

We searched the literature using MedLine, Embase, PubMed, Cochrane Central Register of Controlled Trials, National Health Service Economic Evaluation Database, Health Technology Assessment Centre for Reviews and Dissemination, and Web of Science, for relevant articles published from database inception up to April 2019. The search strategy involved combining terms for ATMPs and economic evaluations using the Boolean 'AND' operator. The search was restricted to studies of human subjects and written in the English language. An additional search of the 'grey' literature contained within the websites of HTA organisations was conducted. Further articles were identified from other related systematic reviews and reference lists of included studies. The full search strategy is detailed below.

(Strimvelis [tw] OR "Autologous chondrocyte implantation" [tw] OR Imlygic [tw] OR Luxturna [tw] OR Yescarta [tw] OR Kymriah [tw] OR tisagenlecleucel [tw] OR "chimeric antigen receptor" [tw] OR CAR-T [tw]) OR Gencidine [tw] OR Oncorine [tw] OR Neovasculgen [tw] OR Zalmoxis [tw] OR tonogenchoncel-L [tw] OR GS010 [tw] OR NSR-REP1 [tw] OR "valoctocogene roxaparvovec" [tw] OR AMT-061 [tw] OR AVXS-101 [tw] OR Generx [tw] OR RT-100 [tw] OR Pexa-Vec [tw] OR Collategene [tw] OR VM202 [tw] OR "LentiGlobin BB305" [tw] OR Lenti-D [tw] OR GSK2696274 [tw]) AND (economics [mh] OR "health technology assessment" [tw]) AND english [la]

Eligibility criteria/study selection

Economic evaluations of ATMPs, reported in full, published in the past 20 years (2000-2019) and in the English language were included. Only full economic evaluations were included (i.e. cost effectiveness, cost utility or cost benefit analyses). Partial economic evaluations (e.g. cost minimisation or cost consequence analyses) were excluded, as were studies only reporting the burden of disease or cost of

illness. We excluded editorials, letters, historical articles, discussion or commentary articles, and evaluations published only as abstracts.

Data extraction

Identified articles were screened by two reviewers independently according to the exclusion and inclusion criteria; firstly by title, followed by abstract, and finally by full article text. Any discrepancies were resolved in discussion with the third reviewer. Extracted data included year and country of publication, clinical indication, ATMP and comparator, method of economic evaluation, time horizon, total intervention and comparator costs, QALY gain, incremental cost-effectiveness ratios (ICERs), results of sensitivity analyses, principal study findings, issues of generalisability, study limitations and key methodological challenges as reported by the authors of each study.

Quality of reporting assessment

Articles were assessed for their quality of reporting by their compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [10]. Studies were scored against each of the 24 checklist items according to whether reporting "fully satisfied," or "did not satisfy" the item requirements. The overall quality of reporting was presented as a percentage score of applicable items. Studies scoring above an arbitrary threshold of 75% were considered to be of higher reporting quality. The quality of reporting of individual items from the checklist is expanded further in the narrative.

Narrative synthesis

A narrative synthesis of the methodological challenges associated with economic evaluations of ATMPs was carried out following the methods of Nagpal et al (2019) [11], and based on the information extracted and judgements made on study quality. This approach synthesises findings from multiple studies and uses the words and text from these studies to produce a summary and explanation of the findings therein.

RESULTS

Search results

In total, 4,514 studies were identified following the initial search. Removal of duplicates resulted in 3,358 potentially relevant articles. Title screening resulted in 115 papers, which further reduced to 35 following abstract screening, and 18 following the review of full article texts. The reasons for exclusion are given in Figure 1. Five additional papers were identified from other sources, resulting in 23 studies being included in the review. The data extracted from the included studies are presented in Tables 1-3.

Study characteristics

The review identified economic evaluations of the following ATMPs: CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), embryonic neural stem cells, tumour infiltrating lymphocytes (TIL), in vitro expanded myoblast (IVM), autologous chondrocyte implantation (ACI) (MACI®), autologous CD34+ cells transduced with a lentiviral vector containing the human adenosine deaminase gene (Strimvelis®), and voretigene neparvovec (Luxturna®).

The main clinical indications included acute lymphoblastic leukaemia, Parkinson's disease, haemophilia, defects of the bladder, knee cartilage lesions, adenosine deaminase deficiency, melanoma, stroke, multiple sclerosis and retinal disease.

Of the identified papers, 16 were cost utility analyses (CUA) [5, 12-26, 36, 37] and five were cost effectiveness analyses (CEA) [27-31]. Most studies used some form of economic modelling, mainly Markov models (8 studies) [12-14, 16, 21, 23-25], but also decision trees [12, 16, 18, 22, 23, 25, 27, 29-31, 36, 37], microsimulation [19], survival modelling [20-21] or the headroom method [28].

The time horizon of included studies varied from 1 year, to lifetime in 12 studies which extrapolated costs and outcomes beyond the available clinical evidence.

Principal study findings

Somatic-cell therapy medicines

There were eight economic evaluations of CAR T-cell therapies, of which six suggested they were cost effective. As a bridge to haematopoietic stem cell transplantation, and adopting the recommended methods of NICE, Hettle et al (2017) [5] estimated an ICER of £49,995 per QALY gained, which exceeds the usual NICE threshold range for cost-effectiveness. Sarkar et al (2019) [19] found that CAR T-cell

therapy (unspecified) for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) increased overall cost by US$528,200 and improved outcomes by 8.18 QALYs, resulting in an ICER of $64,600 per QALY gained from a US payer perspective. Cost effectiveness was established in 94.8% of iterations at a willingness to pay of $100,000 per QALY. In Tice et al (2018) [25] the probability of cost-effectiveness of tisagenlecleucel for childhood B-cell ALL at US$50,000 per QALY was just over 70%. These were consistent with Whittington et al (2018) [31], who estimated an ICER in the range of US$37,000 to $78,000 per QALY gained. The Scottish Medicines Consortium (SMC) [20] appraised the manufacturer's submission of axicabtagene ciloleucel which had an ICER of £57,943 per QALY gained and, given its ultra-orphan status, accepted the greater uncertainty in the economic case. Roth (2018) [37] also assessed axicabtagene ciloleucel and found it to be a potentially cost-effective alternative to salvage chemotherapy. The SMC's appraisal of tisagenlecleucel (Kymriah®) [21] identified an ICER of £49,975 per QALY gained, and was not considered cost-effective.

Other economic evaluations of cell-based therapies include a cost utility analysis by Hjelmgren et al (2006) [13] who claimed that embryonic neural stem cells were cost saving in patients with early-onset Parkinson's disease. Retel et al (2017) [17] report that Tumour Infiltrating Lymphocytes (TIL) is expected to generate more QALYs than its comparator at a lower cost and so is dominant. Intracerebral stem cell implantation in stroke patients was found to be cost saving by Svensson et al (2012) [23], under the assumption that stem cell therapy promotes functional recovery in stroke, improves quality of life and reduces societal costs. Tappenden et al (2010) [24] found that autologous haematopoietic stem cell transplantation had the potential to achieve a level of cost effectiveness that is acceptable to policymakers and health care purchasers, but is largely determined by the interpretation of available clinical effectiveness data and the duration over which such effects may be observed. Vilsboll et al (2018) [29] found in vitro expanded myoblast (IVM) to be dominated by midurethral slings (MUS) treatment (the comparator) but speculated that the cost of the IVM procedure would reduce in the future as the costs of cell expansion reduce.

Tissue-engineered medicines

There were five economic evaluations which of autologous chondrocyte implantation (ACI). One was a cost-effectiveness analysis (Aae et al 2018) [27] which reported that a 1 point increase in clinical scores (patient reported outcome measures) had lower costs for microfracture (MF) than for ACI at 5 years. Among the cost utility analyses, Gerlier et al (2010) [12] showed CondroCelect to be cost-effective compared with MF with an ICER of €16,229 per QALY gained. The main finding in Mistry et al (2017) [15] was that if the decision-maker is willing to pay £20,000 for a QALY, ACI is 56-59% more likely to be cost-effective than MF. Samuelson et al (2012) [18] estimated the *average* cost per QALY for ACI-P to be $9,466 compared with $9,243 for ACI-C; no ICERs were presented. De Windt et al (2018) [30]

compared single-stage cartilage repair (instant allogeneic mesenchymal stromal (stem) cells (MSC) product accompanying autologous chondron transplantation) with microfracture, and estimated the ICER to range from €28,588 to €147,513 per QALY gained. However, compared with ACI, the single-stage procedure was forecast to be cost saving over a 5 year horizon, largely as the cell expansion procedure is rendered redundant.

McAteer et al (2007) [28] utilised the headroom method to guide investment decisions in regenerative medicine. Based on a tissue engineering applications in the urinary tract, they estimated a headroom of around £16,268, but noted the limited market which may reduce potential profitability.

Gene therapy medicines

The cost effectiveness of Strimvelis® was examined in two analyses of which one was deemed to be cost effective. South et al (2018) [22] reported a NICE Highly Specialised Technology Evaluation which estimated the most plausible ICERs for Strimvelis® to be lower than £100,000 per QALY gained. NICE approved Strimvelis® for the treatment of ADA-SCID where a matched related donor is unavailable [16]. In the treatment of severe haemophilia A, Machin et al (2018) [14] found that gene therapy is likely to be cost saving compared with the current standard of care involving FVIII prophylaxis. Zimmerman et al (2019) [26] estimated the ICER for voretigene neparvovec (Luxturna®) for the treatment for vision loss owing to the ultra-rare RPE65-mediated inherited retinal disorders, at $480,100 per QALY gained. This was driven largely by the high cost of treatment and the relatively low gains in QALYs (1.3 over a lifetime), consistent with treatments that are not 'curative' nor extend life expectancy.

Quality of reporting

In terms of reporting, 13 studies [12, 14, 15, 17, 19, 24-26, 29-31, 36] were deemed to be of good quality (Table 4). However, many were incomplete with respect to important methodological detail. The perspective was unclear in seven of the studies [16, 18, 20-22, 27, 28]. Two studies [20, 21] did not state explicitly the modelling approach. Three studies [15, 18, 27] did not mention explicitly a time horizon. Four studies [20, 21, 29, 30] did not specify whether costs and outcomes were discounted. The reporting of sensitivity analysis was more complete, with evidence of deterministic univariate sensitivity analysis and multivariate probabilistic sensitivity analysis having been conducted in the majority of studies, with only two [27, 28] not mentioning any sensitivity analysis. While reporting quality was not analysed by study attributes, such as authorship affiliation, grey versus standard literature or country of origin, there were instances of high variability even within one reporting organisation. Variability in the quality of reporting of manufacturers' submissions to health technology agencies, as one example, is likely to be a function of what can be disclosed publicly, the level of detail provided by the manufacturer

as well as the reporting template used. It is important to recognise that reporting quality may not reflect methodological quality.

Methodological challenges

Size and design of trials

A recurring theme in the literature relates to the small size of clinical trials and the methodological challenges this presents. All ATMPs to date are indicated for rare diseases, which presents a challenge in terms of patient recruitment but nonetheless, trials risk being statistically underpowered. Aae et al (2018) [27] highlighted the small sample sizes in trials which might increase the risk of false negative findings, but perhaps equally important, also reduces the precision of the estimate of treatment effectiveness. Further evidence, including from post-approval studies (e.g. Lam et al 2019) [32] are necessary to reduce uncertainty in key clinical parameters.

Lack of data on disease progression and long term effects

Sarkar et al (2019) [19] discussed how CAR T-cell therapy is a new therapy and so long term data on survival, costs, the role of HSCT after CAR T-cell therapy and complications that could affect the cost effectiveness analysis results are lacking. Mistry et al (2107) [15] noted that the length of follow-up in the published trials of chondral defect in the knee was too short and hence there are no long term data on success and failure rates. Further, because of the paucity of data from clinical studies, transition probabilities may not be calculable for parameterising economic models.

Assumptions about efficacy and comparative effectiveness

Many economic evaluations required strong assumptions about the efficacy and comparative effectiveness of the ATMP, mainly due to the limitations of the available clinical evidence. In Machin et al (2018) [14], for instance, the assumption that successful gene therapy results in full quality of life was not substantiated by evidence, and could introduce significant bias in their estimates of cost-effectiveness. Lin et al (2018) [36] stated, as a limitation, that no high-quality long-term clinical outcomes data existed for tisagenlecleucel. Some evaluations pertained to early phases of drug development, or were analyses of hypothetical drugs with very limited (if any) evidence on treatment effect. No randomised controlled trial data were available to Retel et al (2017) [17], for instance, and therefore data on the effectiveness of Tumor Infiltrating Lymphocytes (TIL) had to be drawn from alternative, lower quality evidence [33, 34]. A lack of comparative evidence limited the economic evaluation of Tice et al (2018) [25] and as evidence on long-term survival was largely unknown, further assumptions had to be made in relation extrapolating beyond the available evidence. The main

limitation in Gerlier et al (2010) [12] was that a Markov model could not be constructed due to there being no robust data on the probability and time to occurrence of clinical events associated with osteoarthritis and total knee replacement. The absence of data was the main limitation also in Tappenden et al (2010) [24], where there was no randomised controlled trial evidence to input into the model; and Vilsboll et al (2018) [29] who reported a lack of uniform reporting tools to define the outcome of stress urinary incontinence interventions. Where strong evidence was not available, authors often relied on expert opinion. In the NICE (2016) [16] review of whether their current methods of economic evaluation are 'fit for purpose' in assessing ATMPs, they used hypothetical datasets to assess CAR T-cell therapy in terms of a bridge to stem cell transplantation and with curative intent. They used theoretical prices that would result in the therapies being valued at the NICE willingness to pay thresholds of cost-effectiveness. Overall, they found that while current NICE methods and processes were indeed robust and relevant for the appraisal of ATMPs, quantification of clinical outcomes and uncertainty were key to their evaluation.

Lack of data on HR-QoL / utilities

The NICE (2017) [15] assessment highlighted the limitation of relying on external data on patient quality of life. Similarly, Samuelson et al (2012) [18] noted a lack of available evidence and resorted to obtaining data on health state utility, as well as outcome scores, graft hypertrophy and failure rates from the literature. Mistry et al (2017) [15] also report a lack of evidence on utility values that could introduce additional uncertainty and potential bias. An absence of reliable data on utilities undermines the robustness of QALY calculations.

Generalisability

The main themes in terms of generalisability relate to costs. Costs of ATMPs obtained from specific hospitals in specific countries, for instance, might limit generalisability to other jurisdictions [13, 17, 18, 27, 30]. This may be due to different methods of production, pricing and service delivery in different settings. Other issues of generalisability highlighted in the reviewed studies, include the transferability of results from a US to a UK setting [25], the importance of age as a variable in potentially curative treatments [14] and using QALYs based on the same multi-attribute health status classification system internationally [29].

Analysts' resolution of methodological challenges

The main methodological challenge was the lack of clinical data with which to inform any modelling or economic evaluation attempted [12, 13, 15, 18, 19, 24, 27, 29, 36]. In all these studies, the problem was addressed by recourse to the published literature, or by making assumptions. For example, Mistry et al

(2017) [15] derived transition probabilities from two studies, which compared MACI (matrix-applied chondrocyte implantation) with MF (MicroFracture), and expert clinical opinion. Tice et al (2018) [25] estimated the time at which long-term survivors would be considered effectively cured based on assumptions that were necessary to extrapolate the survival curve for trial participants. While disease modelling provides a way of estimating long-term effects, this does not substitute for good quality clinical trial evidence.

DISCUSSION

Statement of principal findings

Of the 23 studies identified, 4 [13, 14, 17, 23] had interventions that dominated the comparator (more effective, and cost-saving), while 2 [24, 29] estimated ICERs which indicated that the interventions were dominated by the comparator treatment. The remaining studies had ICERs ranging from £14,395 per QALY gained (for Autogolous Chondrocyte Implantation) in Mistry et al (2017) [15], to USD$610,600 per QALY gained for Instant MSC Product accompanying Autologous Chondron Transplantation (de Windt et al 2018) [30]. The narrative overview of the methodological challenges encountered in the identified papers revealed as the principal difficulties, the paucity of trial data to inform economic analysis, the lack of long-term data on outcomes and costs, and dependence on critical and often unsubstantiated assumptions. The clinical evidence was insufficient in many (if not most) instances to support claims that treatment was curative, which has a major bearing on estimates of survival and quality-adjusted life expectancy required for calculating cost-effectiveness.

Strengths and weaknesses of this review study

The main strength of this review is that it brings together an array of literature concerning the economic evaluation of ATMPs and identifies, from the studies, the main methodological challenges. The search terms were designed to have the maximum likelihood of identifying relevant articles; however there are likely to be many unpublished economic evaluations submitted to HTA organisations, and presented at conferences (although abstracts were excluded explicitly), which were not included in the review. Our language restriction is a further limitation which excluded economic analyses published (or available from HTA organisations) in languages other than English.

Unique features of ATMPs for HTA

Although current methods of economic evaluation are considered by some organisations to be sufficient for analysing ATMPs [5, 16], there may be some unique features of ATMPs that require consideration

when performing such analyses. Hettle et al (2017) [5], for instance, claim the factors that make ATMPs unique as the following: the potentially curative nature of the therapies along with lifetime benefits; the changing nature of the product characteristics over time; potential long-term safety issues; organisational and scaling issues; and the significant up-front cost that face payers.

Whether indeed these are unique to ATMPs is debatable (many surgical interventions have high up-front costs with lasting benefits; antimicrobial treatments are curative; several medicines have potential long-term safety concerns etc.). However, their exceptionally high costs demand higher evidential standards for claims of survival benefits and cure. The issue of whether or not certain ATMPs are curative is still not borne out in the literature. For tisagenlecleucel, the SMC (2019) [21] assumed it to be curative if individuals in the study survived past 24 months. None of the economic evaluations included a value of information analysis to quantify the potential value of longer and larger trials to support the evidence base.

The differential timing in the costs and accrual of benefits associated with ATMPs suggests that time preference, and the choice of discount rate, is likely to be more impactful on their cost-effectiveness compared to many other conventional health technologies. NICE (2017) [16] applied a discount rate of 1.5% per annum for costs and benefits, in accordance with its guidance for treatments that restore people to full or near-full health when they would otherwise die [35]. Gerlier et al (2010) [12] highlighted a particular problem in their evaluation of the ATMP, ChondroCelect. Their application of a higher discount rate for costs than for effects meant that when the need for total knee replacement among patients with osteoarthritis receiving ChondroCelect increased, the ICER reduced in favour of ChondroCelect. However, the best treatment for the patient is the one that minimises pain and discomfort and avoids the need for knee replacement in the first place. This type of paradox could be encountered in other contexts and should be taken in to consideration when conducting economic evaluations of ATMPs.

CONCLUSION

This systematic review is a comprehensive account and methodological critique of economic evaluations of ATMPs. In particular, it provides a narrative synthesis of the challenges facing health technology analysts and economists in the evaluation of ATMPs. The main issue identified was the paucity of long-term clinical trial data to inform cost effectiveness analyses. This was the case in eleven of the 23 papers identified. Analysts had to resort to strong assumptions about the curative nature of ATMPs and their ability to return patients to full health-related quality of life. Such assumptions can lead to biased estimates of cost-effectiveness and inefficient allocation of resources. There are also

implications for the funding of ATMPs, especially in terms of outcomes-based payment, which depends critically on the measurement of treatment success.

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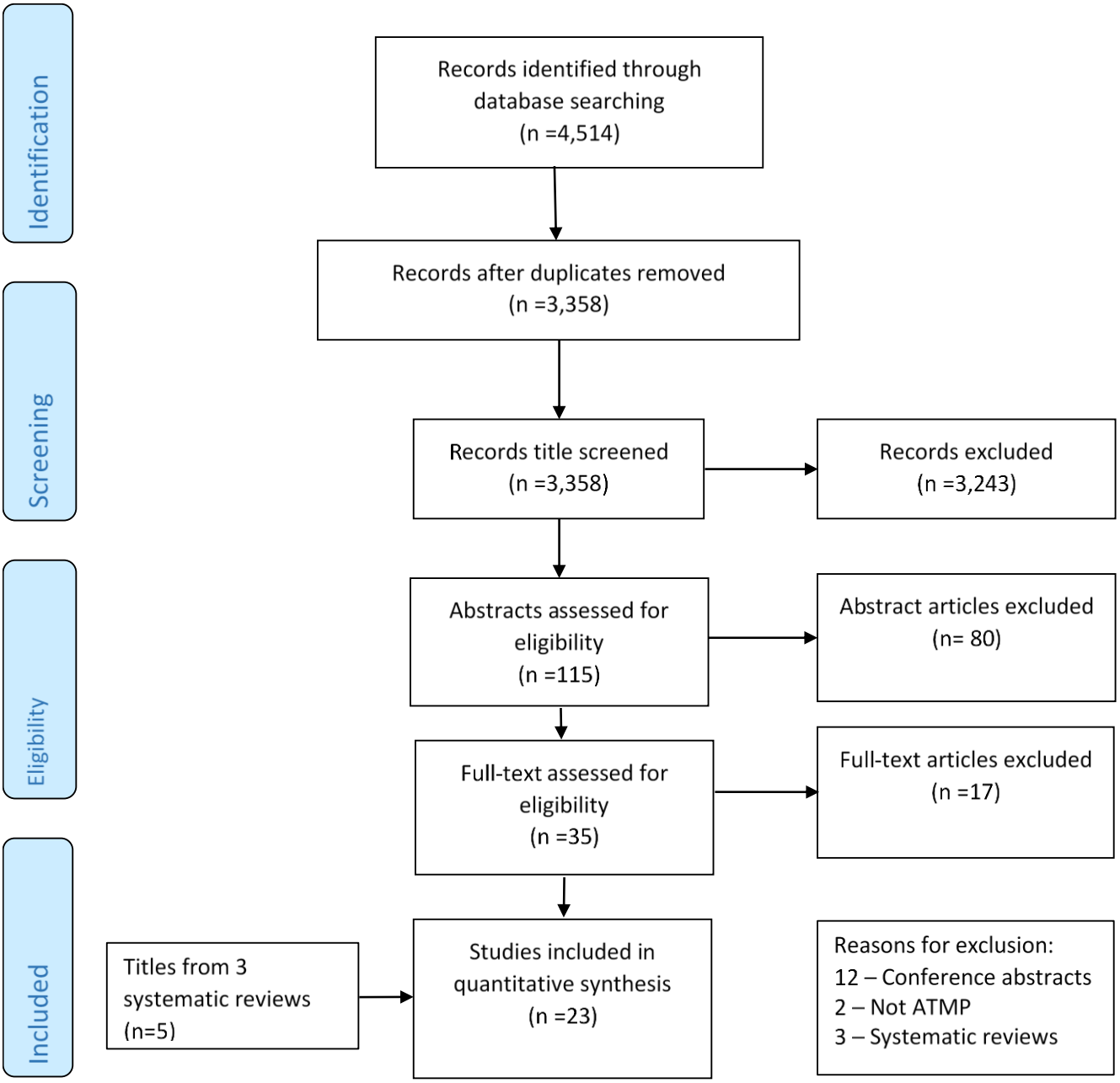

Figure 1: PRISMA flowchart for this review

Table 1: Principal characteristics of included studies

Reference	Year	Country (currency)	Clinical Indication	ATMP	Comparator	Method	Time horizon
Somatic-cell therapy medicines							
[5]	2017	UK (GBP £)	Acute lymphoblastic leukaemia	CAR T-Cell Therapy (unspecified)	Standard of Care	CUA (Conventional assessment of cost-effectiveness at the patient level)	Lifetime
[13]	2006	Sweden (Euro €)	Parkinson's disease	Embryonic neural stem cells	Standard pharmacological therapy	CUA (Markov state transition model)	25 years
[17]	2017	Netherlands (Euro €)	Metastatic melanoma	Tumor Infiltrating Lymphocytes	Ipilimumab	CUA (Markov decision model)	Lifetime
[19]	2019	USA (USD $)	Relapsed/refractory B-cell acute lymphoblastic leukemia	CAR T-Cell Therapy (unspecified)	Standard Of Care	CUA (Microsimulation model)	n/a
[20]	2018	Scotland (GBP £)	Relapsed or refractory diffuse large B cell lymphoma and primary mediastinal large B cell lymphoma	Axicabtagene ciloleucel	Best supportive care	CUA (Three-state partitioned survival model)	Lifetime
[21]	2019	Scotland (GBP £)	Relapsed or refractory diffuse large B-cell lymphoma	Tisagenlecuecel	Salvage chemotherapy regimens	CUA (Cohort-based partitioned survival model)	46 years
[23]	2012	Sweden (Euro €)	Stroke	Intracerebral stem cell implantation	Standard post stroke care	CUA/CBA (Decision tree model)	Lifetime
[24]	2010	UK (GBP £)	Multiple sclerosis	Autologous haematopoietic stem cell transplantation	Mitoxantrone	CUA (Markov modelling)	1 year

[25]	2018	USA (USD $)	Childhood B-Cell Acute Lymphoblastic Leukemia	Tisagenlecleucel	Clofarabine	CUA (Decision tree and long-term semi-Markov partitioned survival model)	Lifetime
[29]	2018	Denmark (Euro €)	Female stress urinary incontinence	In vitro expanded myoblast (IVM)	Midurethral slings	CEA (Decision tree)	5 years
[31]	2018	USA (USD $)	Pediatric Patients With Relapsed or Refractory Leukemia	Tisagenlecleucel	Clofarabine	CEA (Decision analytic model)	Lifetime
[36]	2018	USA (USD $)	Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia	Tisagenlecleucel	Blinatumomab, clofarabine combination therapy	CUA (Markov modelling)	Lifetime
[37]	2018	USA (USD $)	Relapsed or refractory large B-cell lymphoma	Axicabtagene ciloleucel	Salvage chemotherapy	CUA (Decision model)	Lifetime
Tissue engineered medicines							
[27]	2018	Norway (Euro €)	Focal cartilage defects in the knee	Autologous chondrocyte implantation	Microfracture	CEA (Decision tree)	5 years
[12]	2010	Belgium (Euro €)	Knee cartilage lesions	ChondroCelect used in ACI	Microfracture	CUA (Decision tree)	40 years
[28]	2007	UK (GBP £)	Urethral defects and bladder resection for cancer	Tissue engineering	Ileocystoplasty	CEA (Headroom Method)	n/a
[15]	2017	UK (GBP £)	Chondral defect in the knee	Autologous chondrocyte implantation	Microfracture	CUA (Markov state transition model)	Lifetime
[18]	2012	USA (USD $)	Articular cartilage injury	ACI collagen patch	ACI periosteal patch	CUA (Decision analytic model)	Lifetime
[30]	2018	Netherlands (Euro €)	Articular cartilage repair	Instant MSC Product accompanying	MicroFracture & Autologous	CEA (Decision tree)	Lifetime

				Autologous Chondron Transplantation (IMPACT)	chondrocyte implantation		
Gene therapy medicines							
[14]	2018	USA (USD $)	Haemophilia	Gene therapy	Prophylaxis with factor VIII	CUA (Markov state transition model)	10 Year
[16]	2017	UK (GBP £)	Adenosine deaminase deficiency-severe combined immunodeficiency	Strimvelis® Haematopoietic stem cell transplant	Matched unrelated donor	CUA (Decision tree)	n/a
[22]	2018	UK (GBP £)	Adenosine deaminase deficiency-severe combined immunodeficiency	Strimvelis®	Haematopoietic stem cell transplant	CUA (Decision tree & Markov modelling)	Lifetime
[26]	2019	USA (USD $)	Biallelic RPE65- Mediated Inhereted Retinal Disease	Voretigene neparvovec	Standard of care	CUA (2 State Markov Model)	20 years

Abbreviations: ATMP Advanced Therapy Medicinal Product; CAR Chimeric antigen receptor; ACI Autologous chondrocyte implantation; MSC allogeneic mesenchymal stromal (stem) cells; CUA cost-utility analysis; CBA cost-benefit analysis; CEA cost-effectiveness analysis

Table 2: Main results of included studies

Reference	Total Intervention Cost	Total Comparator Costs	QALY gain	ICER[1]/Cost per point improvement in outcome*/ Headroom[2]	Sensitivity Analysis
Somatic-cell therapy medicines					
[5]	£449,128	£75,962	8.82-1.36 = 7.46	£49,995[1]	If the discount rate for costs and outcomes was reduced to 1.5% then the cost per QALY would be reduced to £35,162.
[13]	HY stage III: €156,467 HY stage IV: €163,588	HY stage III: €158,943 HY stage IV: €186,279	HY stage III: 0.873 HY stage IV: 1.133	Intervention cost saving	Univariate analysis: time horizon (10,20,30 years); discount rate (0%, 5%); treatment efficacy (±50%); occurrence of complications (±100%); analytical perspective (direct medical costs only vs. including other direct costs); method of determining utilities. The ICER was cost saving for most variables with the exception of post-operative disease progression where it was cost increasing
[17]	€62,000	€91,487	0.07	Intervention dominates ICER n/a	The parameters with the most impact on the incremental costs were survival, drop-outs and costs of treatment. For the incremental QALYs, these were survival and utilities.
[19]	$968,800	$440,600	16.76-8.58 = 8.18	$64,600[1]	If the 1-year survival dropped below 57.8% then the ICER rose above $100,000 per QALY, and CAR T-cell therapy would not be considered cost effective.
[20]	£1,035,601	£405,126	31.3-22.8 = 8.5	£74,430[1]	No sensitivity analysis performed.
[21]	Not Reported	Not Reported	4.1	£57,943	The results are associated with increased uncertainty when key variables in the model were revised.
[23]	$202,901	$221,956	1.34	Intervention is cost saving	Univariate analysis: relative efficacy of SCT; mode of transplantation; age at stroke onset; annual risk of recurrent stroke; SCT procedure risk of death; intervention on mRS3/4;

					extended leave period. The highest ICER came with Intervention on mRS 4.
[24]	£131,666	£107,126	4.1-5.12= -1.02	Intervention is dominated	Univariate analysis: transplant related mortality rate (0/1.3%); relative PFS hazard ratio between HSCT and mitoxantrone; tariff cost of HSCT (±25%), costs of managing multiple sclerosis (±25%); discount rate (0/3.5%). The ICER is most sensitive to the cost of transplantation itself.
[25]	$666,754	$337,256	9.28-2.10 = 7.18	$45,871[1]	Uncertainty around long-term survival was explored through variation in the discount rate used in the sensitivity analysis
[29]	€2,224	€1,223	0.11	Negative ICER. Intervention dominated by comparator	One-way sensitivity analysis based on the upper limit cure rate for in vitro expanded myoblasts indicates that this may become more effective as compared with the standard midurethral slings procedure.
[31]	$667,000	$337,000	9.28	$46,000[1]	Across scenario analyses that included more conservative assumptions regarding long-term relapse and survival, the ICER ranged from $37,000 to $78,000 per QALY gained.
[36]	$599,000	$374,000	12.1	$61,000[1]	In probabilistic sensitivity analyses, tisagenlecleucel at a 5-year relapse-free survival rate of 40% was cost effective in 99.3%, 98.7%, and 6.0% of simulations at willingness to pay thresholds of $150,000, $100,000, and $50,000, respectively
[37]	$552,921	$172,737	7.67 - 1.13 = 6.54	$55,128[1]	Scenario analyses in which patients in remission had mortality rates 10% and 20% higher than the age-matched general US population. Cost-effectiveness was most sensitive to the fraction achieving long-term remission, discount rate, and axi-cel price.
Tissue engineered medicines					
[27]	€14,238	€4,329	Not Reported	€2,134[*]	A 66% reduction in the total costs following ACI or a 190% increase in the total costs of microfracture led to equivalent total costs at 5 years
[12]	€24,879	€1,035	1.282	€16,229[1]	Probabilistic sensitivity analysis showed that 80% of simulations were below a threshold of €22,000 per QALY

[28]	Not Reported	Not Reported	Not Reported	£16,268[2]	n/a
[15]	£17,740	£3,020	n/a	£14,395[1]	Cost of cells for ChondroCelect were £16,000. Sensitivity analysis was conducted to vary this figure by reducing the costs by 25%, 50% and 75%. The time horizon was also varied by 10, 20, 30, 40 and 50 years. The cost of cells are a key driver for the ICER.
[18]	$66,752	$66,939	0.07	$9,466 (average cost-effectiveness ratio)	Sensitivity analysis was performed regarding the additional cost of the type I/III collagen patch ($780) in ACI-C as well as the rate of graft hypertrophy after ACI-P (25%). Small changes in outcome affects the ICER substantially so that ACI-P becomes more cost effective if the utility value of patients doing well after ACI-P is increased slightly from 0.85 to 0.86 or that of ACI-C is decreased slightly from 0.85 to 0.84.
[30]	€11,797	€6,081 (MF)	0.04	€610,600[1]	If the utilities of IMPACT were 10% lower than ACI, the maximum costs of IMPACT would be €23,697
Gene therapy					
[14]	$1,022,049	$1,693,630	8.33 - 6.62 = 1.71	Intervention dominates ICER n/a	Only variation of gene therapy cost caused the gene therapy strategy to be no longer cost saving compared with prophylaxis
[16]	Not Reported	Not Reported	13.6	£36,360[1]	NICE evidence review group proposed a list of changes to be included as a sensitivity analysis. These increased the ICER from the company base case to £86,815 per QALY gained.
[22]	Not Reported	Not Reported	n/a	£49,975[1]	The results are associated with increased uncertainty when key variables in the model were revised.
[26]	$1,039,000	$213,400	1.3	$480,100[1]	For different levels of visual ability the ICER and the necessary discount to reach a defined willingness to pay threshold was calculated. The ICER decreased with increasing visual ability at baseline.

Abbreviations: QALY quality-adjusted life year; ICER incremental cost-effectiveness ratio; HY Hoehn and Yahr (scale); CAR Chimeric antigen receptor; SCT stem cell transplant; mRS modified Rankin Scale; PFS progression-free survival; HSCT Haematopoietic stem cell transplantation; ACI Autologous chondrocyte implantation; IMPACT Instant allogeneic mesenchymal stromal cells Product accompanying Autologous Chondron Transplantation

Table 3: Principal findings, issues of generalisability, limitations and methodological challenges of included studies as reported by study authors

Reference	Study findings	Generalisability	Limitations	Key methodological difficulties
Somatic-cell therapy medicines				
[5]	Main purpose was to report the potential cost-effectiveness of CAR T-cell therapy; and to highlight key uncertainties surrounding these results.	Not reported.	This exercise was conducted on theoretical data and assumed costs, and may not capture the problems associated with real world data.	Although evidence about ATMPs is expected to be associated with uncertainty in determining the long-term costs and benefits to patients and the NHS, existing methods available to estimate the implications of this uncertainty are sufficient. Challenges include: the potential curative nature and claims of long-term/lifetime benefits; the potentially rapid changes that may arise in product characteristics over time; potential longer-term patient safety issues because of persistence; organisational and scaling issues; and the potentially significant upfront costs that may arise.
[13]	Long-term cost savings in most instances in early onset Parkinson's disease patients in HY stages III-IV.	The model was based on the Swedish health care system, but devised to be applicable to available data on treatment costs and health state utilities for different HY stages. Such data are now available from a variety of countries.	Small number of patient-level data; clinical effectiveness data based on open-label transplantation trials	The frequent use of placebo as a comparator, together with the extra attention given to randomised control trial patients may contribute to non-representative outcomes. Use of real life observations claimed to be less restricting to allow hypothetical comparisons between standard therapy and a range of different alternatives.

[17]	Tumour infiltrating lymphocytes is expected to generate more QALYs than its comparator at a lower cost and so dominates.	The prices of treatments vary substantially between countries. This reduces the generalisability of the results.	No clinical trial data available and therefore data on the effectiveness of tumour infiltrating lymphocytes had to be drawn from various sources.	It is unknown which patient subgroup had the best response to tumour infiltrating lymphocytes.
[19]	CAR T-cell therapy increased overall cost by $528,200 and improved effectiveness by 8.18 QALYs, which produced an ICER of $64,600 per QALY per payer perspective. Cost effectiveness was established in 94.8% of iterations at a willingness to pay of $100,000 per QALY.	Not reported.	CAR T-cell therapy is a new therapy and thus long-term data on survival, costs, role of HSCT after CAR-T, and complications that could influence these cost effectiveness analysis results are lacking. Model inputs including costs and utilities from heterogeneous sources.	Used a microsimulation model rather than a Markov model, permitting more complex model design than traditional Markov models.
[20]	As axicabtagene ciloleucel is an ultra-orphan medicine, Scottish Medicines Consortium can accept greater uncertainty in the economic case, despite a base case ICER of £57,943 per QALY gained.	Not reported.	The absence of any directly comparative data.	Longer term data are required to confirm whether axicabtagene ciloleucel is a curative treatment.
[21]	The intervention produced an ICER of £49,975 per QALY gained when compared to chemotherapy regimen Gen-Ox which is under the NICE £50,000 threshold	Not reported.	Haematological Malignancy Research Network data were used to estimate overall survival for chemotherapy patients meaning that a naïve indirect comparison was used as the basis of the estimation	An assumption was made that that patients who were alive at 24 months were effectively cured.

			of clinical outcomes in the economic model.	
[23]	A potential for long-term cost savings by reducing the disability after stroke; societal value up to US $166,500 (US $184,567), particularly in younger patients with stroke with moderate disability, with possible cost effectiveness estimated down to relative efficacy of 14%.	Enables cost benefit analysis for patients with stroke under a wide range of assumptions	Effectiveness of SCT was based on expert opinion; did not include differential costs of early vs. late administration post-stroke; limited standard care data reflecting survival, treatment patterns, and transition probabilities for mRS.	Ideally health economic analyses are based on long term data. If this is not available, and for most treatments only short term data is available, disease modelling provides a way of estimating long term effects.
[24]	A potential to achieve a level of cost effectiveness that is acceptable to policymakers and health care purchasers, but is largely determined by the interpretation of available clinical effectiveness data and the duration over which such effects may be observed.	The focus of the analysis was on the potential cost effectiveness of autologous HSCT in the management of secondary progressive multiple sclerosis only.	The absence of direct randomised controlled trial evidence to input into the model.	Modelling cannot be considered a substitute for good quality clinical trial evidence.
[25]	Total cost for tisagenlecleucel was double that of clofarabine while the gains in QALYs of tisagenlecleucel was four times that of clofarabine. The probability of cost-effectiveness at $50,000 per QALY was about 0.7.	Cost perspective specific to US payer which may not be generalizable to other settings.	This analysis was limited primarily by the lack of comparative evidence available for these therapies. Evidence on long-term effectiveness is still unknown, which resulted in assumptions being made related to trial survival curve extrapolation and the time	The authors closely followed the methodology used in the 'curative intent' mock evaluation of CAR T-cell therapy [5]. The differences in estimates between the two models are likely due to the use of two different approaches to curve extrapolation.

			point at which long-term survivors would be considered effectively cured.	
[29]	IVM is dominated by MUS treatment but as costs of cell expansion are likely to reduce in the future this may reduce the cost of the IVM procedure.	Using QALYs based on the same multi-attribute health status classification system internationally would aid generalisability.	Lack of uniform reporting tools to define outcome of stress urinary incontinence interventions. When robust evidence was not available, the estimates relied on expert opinions.	Concerns about the sensitivity of generic multi-attribute health outcomes measures in the context of urinary incontinence.
[31]	The cost-effectiveness likely is between $37,000 and $78,000 per QALY gained over a patient's lifetime horizon.	Not reported.	Lack of evidence for the comparator which affects the calculation of the ICER. Due to limited follow up, assumptions had to be made about long-term survival and when a patient is effectively cured.	Flattening in the tail of the survival curves was observed for both tisagenlecleucel and clofarabine. Standard parametric models likely underestimate survival when flattening in the tail exists; therefore, they used a flexible parametric model to account for this flattening.
[36]	Reduction of the price of tisagenlecleucel to $200,000 or $350,000 would allow it to meet a $100,000 or $150,000 per QALY willingness-to-pay threshold in all scenarios.	Not reported	No high-quality long-term clinical outcomes data exist for tisagenlecleucel	The authors addressed the main limitation by modelling multiple long-term effectiveness scenarios, including one where all patients eventually experience relapse.
[37]	The likelihood that axi-cel is cost-effective was 95% at a willingness to pay of $100,000 per QALY.	Not reported	The current data of the ZUMA-1 trial is limited at a median follow up of 15.4 months.	As this analysis used axi-cel 1-year follow-up data, the authors find it prudent to re-examine cost effectiveness after additional follow-up.
Tissue engineered medicine				

[27]	For all measures, a 1-point increase in clinical scores had lower costs for microfracture than for ACI at 5 years.	Unit prices came from a single orthopaedic hospital which may limit the generalisability of the findings.	Small study population leading to bias. MF group had slightly smaller lesions meaning that they are more responsive to physiotherapy.	Clinical uncertainty limits robustness of economic analysis.
[12]	ChondroCelect shown to be a cost-effective strategy compared with microfracture and the ICER is below the NICE threshold.	Not reported.	Absence of firm data on the probability and time to occurrence of osteoarthritis total knee replacement. Therefore a Markov model was not possible.	When the need for TKR increases, ICER expected to decrease in favour of ChondroCelect. Due to higher discount rates for costs rather than effects, the procedure resulting in more TKR patients would also generate more QALYs. However, for the patient the optimal treatment is one that minimizes pain and discomfort and avoids the need for TKR. Long-term data are needed to characterise specific events.
[28]	The headroom for tissue-engineered bladder was estimated at around £16,268. However, the market size is limited reducing potential profitability.	Not reported.	Not reported.	The headroom method is claimed to inform decisions without the need for complex modelling which may have very wide parameter uncertainty. In the case of a technology yet to be developed, or in early stages of development, the very nature of the product is uncertain, leading to difficulties in its economic evaluation; although the method proposed is a simple cost utility analysis.
[15]	If the decision-maker is willing to pay £20,000 for a QALY, ACI is 56-59% more	Not reported.	The length of clinical trial follow-up was too short and hence, there are no long-term	There is a clear lack of evidence on health state utility values for

	likely to be cost-effective than microfracture.		data on the success and failure rates. Because of the paucity of data from clinical studies, transition probabilities were not available for each transition in the model.	patients that have had cartilage defects of the knee.
[30]	IMPACT can be dominant to ACI over a 5 year horizon in terms of cost effectiveness	All costs were derived from the hospital administration data and/or from other Dutch data resources, which may limit its transferability to other settings.	Patients included in these models, who reflect randomised controlled trial populations, are not always typical of patients seen in orthopaedic sports practice.	Included only a small number of patients from a randomised controlled trial with a follow-up of 5 years. Greater patient numbers and a longer follow-up period will make such an early analysis more reliable.
Gene therapy				
[15]	Treatment with gene therapy is likely to be cost saving for the treatment of severe haemophilia A compared with the current standard of care with Factor VIII prophylaxis.	Age is an important variable in potentially curative treatments. The results are generalizable to different age groups because altering the probability of death, a good approximation for changes in age, did not significantly alter the cost-effectiveness of gene therapy.	The assumption that successful gene therapy results in full quality of life could potentially bias results toward gene therapy. The lack of commercially available gene therapy for haemophilia A. Limiting the time frame to 10 years reduces the cost-effectiveness of gene therapy significantly.	The assumption that gene therapy leads to full quality of life could potentially bias the results towards gene therapy.
[17]	The ICER for Strimvelis® is below the £100,000 per QALY cost-effectiveness	Not reported.	Quality of life data had to be collected from the literature.	Discount rate was 1.5% per annum as the treatment comes under the definition NICE uses for a treatment that restores people to full or near-

	threshold for highly specialised technologies.			full health when they would otherwise die.
[23]	The most plausible ICERs were lower than £100,000 per QALY gained and that Strimvelis® should be recommended for treatment of ADA-SCID where a matched related donor is unavailable.	Not reported.	Given the rarity of the disease, there were some issues with the representativeness of the population that had received Strimvelis® to the eligible population in England.	While there is a well-developed methodological literature for evaluating randomised controlled trials in much larger patient populations, there is less guidance on assessing study designs most appropriate for evaluating specialised technologies in rare conditions.
[26]	The high ICER is driven by the high cost of voretigene neparvovec and the relatively low gains in QALYs. Voretigene neparvovec does not improve survival and is not 'curative'. QALY gains come from quality of life improvements.	Not reported.	Used utility values from other retinal disease population as quality of life data for RPE65-mediated retinal disease does not exist. This may have led to biased outcomes.	Without long-term data, it cannot be known how long benefit will be maintained.

Abbreviations: CAR Chimeric antigen receptor; ATMP Advanced Therapy Medicinal Product; HSCT Haematopoietic stem cell transplantation; SCT stem cell transplant; IVM in vitro expanded myoblasts; MUS midurethral slings; ACI Autologous chondrocyte implantation; TKR total knee replacement; IMPACT Instant allogeneic mesenchymal stromal cells Product accompanying Autologous Chondron Transplantation; ADA-SCID Adenosine deaminase severe combined immunodeficiency; HY Hoehn and Yahr (scale); mRS modified Rankin Scale; NHS National Health Service; QALY quality-adjusted life year; ICER incremental cost-effectiveness ratio

Table 4: Quality Reporting using CHEERS [10]

Reference →	[28]	[13]	[5]	[14]	[15]	[29]	[16]	[17]
Title	0	1	1	0	1	1	1	0
Abstract	1	1	1	0	0	1	1	0
Background and objectives	0	1	1	1	1	0	1	1
Target population and subgroups	0	0	1	1	1	0	1	1
Setting and location	0	0	1	0	0	0	0	1
Study perspective	0	1	1	1	1	0	1	0
Comparators	1	1	1	1	1	1	1	0
Time horizon	1	1	1	1	1	0	1	0
Discount rate	1	1	1	1	1	0	1	1
Choice of health outcomes	1	1	1	0	1	0	1	1
Measurement of effectiveness	1	1	1	0	1	0	1	1
Measurement and valuation of preference-based outcomes	1	1	1	1	0	0	0	0
Estimating resources and cost	1	1	1	1	1	1	1	1
Currency, price date and conversion	1	1	1	0	0	0	1	1
Choice of model	1	1	1	1	1	1	1	1
Assumptions	1	1	1	1	1	1	1	1
Analytic methods	1	1	1	1	1	1	1	0
Study parameters	1	1	1	0	1	1	1	0
Incremental costs and outcomes	0	1	1	1	1	0	1	1
Characterising uncertainty	0	1	1	1	1	0	1	1
Characterising heterogeneity	0	0	0	0	0	0	1	0
Study findings, limitations, generalizability and current knowledge	1	1	1	1	1	0	1	0
Source of funding	1	1	0	0	1	1	1	1
Conflict of interest	1	1	1	0	1	1	1	1
Mean score (%)	66.7	87.5	91.7	58.3	79.2	41.7	91.7	58.3

Reference →	[18]	[19]	[20]	[21]	[22]	[23]	[24]
Title	1	1	1	0	0	0	0
Abstract	1	1	1	0	0	0	1
Background and objectives	1	1	1	1	1	1	1
Target population and subgroups	0	0	0	0	0	0	0
Setting and location	0	0	0	0	0	0	0
Study perspective	1	0	1	0	0	0	1
Comparators	1	1	1	1	1	1	1
Time horizon	1	1	0	1	1	1	1
Discount rate	1	1	1	0	0	1	1
Choice of health outcomes	1	1	1	1	1	1	0
Measurement of effectiveness	1	1	1	1	1	0	0
Measurement and valuation of preference-based outcomes	1	0	1	1	1	1	1
Estimating resources and cost	1	1	1	1	1	1	1
Currency, price date and conversion	1	0	0	0	0	0	1
Choice of model	1	1	1	0	0	1	1
Assumptions	1	1	1	0	0	1	1
Analytic methods	1	1	1	0	0	1	1
Study parameters	1	0	1	0	0	0	1
Incremental costs and outcomes	1	1	1	1	1	1	1
Characterising uncertainty	1	1	1	1	1	1	1
Characterising heterogeneity	0	0	0	0	0	0	0
Study findings, limitations, generalizability and current knowledge	1	1	1	0	0	1	1
Source of funding	1	1	1	0	0	1	0
Conflict of interest	1	1	1	0	0	1	0
Mean score (%)	87.5	70.8	79.2	37.5	37.5	62.5	66.7

Reference →	[25]	[26]	[30]	[31]	[32]	[27]	[36]	[37]
Title	1	1	1	1	0	1	1	1
Abstract	0	0	1	0	1	1	1	1
Background and objectives	1	1	1	1	1	1	1	0
Target population and subgroups	1	1	0	0	0	1	1	0
Setting and location	0	0	1	0	0	1	1	1
Study perspective	1	1	1	1	1	1	1	1
Comparators	1	1	1	1	1	1	1	1
Time horizon	1	1	1	1	1	1	1	1
Discount rate	1	1	0	1	1	1	1	0
Choice of health outcomes	1	1	1	1	1	1	1	1
Measurement of effectiveness	1	1	1	1	1	0	0	1
Measurement and valuation of preference-based outcomes	1	1	1	1	1	1	1	0
Estimating resources and cost	1	1	1	1	1	1	1	1
Currency, price date and conversion	0	1	0	0	0	1	1	0
Choice of model	1	1	1	1	1	1	1	1
Assumptions	1	1	1	1	1	1	1	0
Analytic methods	1	1	1	1	1	1	1	1
Study parameters	1	1	1	1	1	0	0	1
Incremental costs and outcomes	1	1	1	1	1	1	1	1
Characterising uncertainty	1	1	1	1	1	1	1	1
Characterising heterogeneity	0	0	0	0	0	0	0	0
Study findings, limitations, generalizability and current knowledge	1	1	1	1	1	1	1	1
Source of funding	0	0	0	0	1	1	0	0
Conflict of interest	1	1	1	1	1	0	0	0
Mean score (%)	79.2	83.3	79.2	75.0	79.2	83.3	79.2	62.5

Systematic Review of Pricing and Funding Mechanisms for ATMPs: An International Perspective

Summary

BACKGROUND The managed introduction of Advanced Therapy Medicinal Products (ATMPs) to the NHS represents a specific challenge, not least because of their exceptionally high prices. Experience from other countries and healthcare settings, as well as the published views of key opinion leaders were reviewed.

METHODS A systematic literature review of economic evaluations of ATMPs, including gene therapies, somatic cell therapies, and tissue-engineered products, was conducted. Literature was searched using MedLine, Embase, PubMed, Cochrane Register, the NHS Economic Evaluation Database and the grey literature of HTA organisations with search terms relating to ATMPs and economic evaluations. Titles were screened independently by two reviewers. Articles deemed to meet the inclusion criteria were screened independently on abstract, and full texts reviewed. Study findings were described thematically.

RESULTS Eighteen articles met the inclusion criteria. Themes from within each article were categorized according to whether they discussed matters relating to: i) research and development, manufacturing and production costs; ii) regulation (licensing and marketing authorization); iii) pricing; iv) health technology assessment; v) market access; and vi) reimbursement. These are critiqued, with reference to the principal points of relevance to the pricing and funding of ATMPs.

CONCLUSIONS There are significant policy issues, including the level at which payers of healthcare are willing to fund ATMPs, the methods of evaluation, the need to challenge how these treatments are priced by the pharmaceutical industry and what prioritization trade-offs the NHS is willing to make in order to implement. There are significant uncertainties especially in terms of patient benefit. There is a need to develop alternative methods of managing costs, such as annuity or amortization of payments over a fixed time-period, and innovative outcomes-based performance payments.

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) which include gene and somatic-cell therapies and tissue-engineered medicines, have the potential to transform current care pathways by offering durable and potentially curative outcomes. However, they are exceptionally expensive, with prices exceeding £1m per patient in some cases. With an expectation that a large number of ATMPs will soon gain marketing authorization (global market is estimated to reach £9bn to £14bn by 2025), healthcare payers and providers face a number of challenges to facilitate patient access to this new category of medicines [1].

There are currently 10 ATMPs available within the European Union and, with more expected to gain market authorization, concerns have been expressed about the significant cost to healthcare payers, including the National Health Service (NHS) in the UK. There is a risk that ATMPs will either not be affordable or other treatments and services may need to be displaced in order to fund them. In addition, healthcare services in the UK are not currently configured to accept, adopt and deploy these therapies routinely.

The aim of this review was to understand the HTA community's current direction with respect to the health technology assessment and appraisal of ATMPs. This will build on the recent review by CADTH, by searching for and requesting: (i) international organizations' specific guidance to manufacturers intending to submit for HTA approval, policies for decision makers with respect to appraisal, and procedures for the appraisal process; and (ii) professional or network organization documentation (e.g. INAHTA, EUnetHTA, ISPOR, HTAi). Evidence on the processes and criteria for decision-making were extracted from these documents, and common themes identified.

METHODS

Reporting

The review methods are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [2].

Review question

The principal review question was: What are the main challenges and solutions for the pricing and funding of advanced therapy medicinal products (ATMPs)?

Search strategy

We searched the literature using MedLine, Embase, PubMed, Cochrane Central Register of Controlled Trials, National Health Service Economic Evaluation Database, Health Technology Assessment Centre for Reviews and Dissemination, and Web of Science, for relevant articles published from database inception up to April 2019. The search strategy involved combining terms for ATMPs and economic evaluations using the Boolean 'AND' operator. The search was restricted to studies of human subjects and written in the English language. An additional search of 'grey' literature contained within the websites of HTA organizations was conducted. Further articles were identified from other related systematic reviews and reference lists of included studies

Search terms

((Advanced therapy OR ATMP OR gene therapy OR cell therapy OR tissue engineered OR regenerative OR Strimvelis OR Autologous chondrocyte implantation OR Imlygic OR Luxturna OR Yescarta OR Kymriah OR Tisagenlecleucel OR chimeric antigen receptor OR Car-T OR Gencidine OR Oncorine OR Neovasculgen OR Zalmoxis OR Tonogenchoncel-L OR GS010 OR NSR-REP1 OR Valoctocogene roxaparvovec OR AMT-061 OR AVXS-101 OR Generx OR RT-100 OR Pexa-Vec OR Collategene OR VM202 OR LentiGlobin BB305 OR Lenti-D OR GSK2696274) AND (economics OR health Technology Assessment OR cost effectiveness analysis OR cost utility analysis OR cost benefit analysis)) AND English [la]

Eligibility criteria/study selection

Editorials, letters, historical articles, discussion or commentary articles discussing the funding, pricing and economics of ATMPs published in the past 20 years (2000-19) and in the English language were included.

Data extraction

Identified articles were screened by two reviewers independently according to the exclusion and inclusion criteria; firstly by title, followed by abstract, and finally by full article text. Any discrepancies were resolved in discussion with the third reviewer. Extracted data included year and country of publication, the objectives of the study, the main findings, limitations and conclusion.

Narrative synthesis

A narrative synthesis was carried out following the methodology of NICE [3], and based on the information extracted and judgements made on study quality. This approach synthesizes findings from multiple studies and uses the words and text from these studies to produce a summary and explanation of the findings therein.

RESULTS

Eighteen articles met the inclusion criteria (Figure 1). Themes from within each article were categorized according to whether they discussed matters relating to: i) research and development, manufacturing and production costs; ii) regulation (licensing and marketing authorization); iii) pricing; iv) health technology assessment; v) market access; and vi) reimbursement. These are critiqued below, with reference to the principal points of relevance to the overarching question concerning the challenges and solutions of pricing and funding of ATMPs.

DISCUSSION

Research and development, manufacturing and production costs

Hampson et al (2017) noted that it is not clear whether payers should include considerations of R&D and manufacturing costs in their assessment of value and reimbursement. They claimed that 'without high per-patient prices, and/or longer-term market exclusivity, ATMPs may not be developed.'

According to Abou-el-Enein (2016) [5] there is a paucity of information about the costs of operation of ATMPs and this complicates the prediction of the investment needed to translate the innovations to the clinic other than as small-scale clinician-led prescriptions. They discuss a cost model that outlines the fixed and variable cost of manufacturing a specific ATMP, CMV specific T-cell immunotherapy. ATMPs need to compete with small molecule pharmaceuticals and so need to demonstrate superior safety and efficacy. By setting a market price for ATMPs companies, they argue, must be ambitious and take account of complex supply logistics needed to scale out rather than scale up production. It is suggested that new and bespoke economic models are needed that focus on operational efficiency while simultaneously reducing the risks involved in production. Such a model was the Clean Technology Assessment Technique (CTAT) which integrates manufacturing economics and optimization approaches to arrive at an optimal cost for producing specific ATMPs. This model attempts to estimate the cost of goods. The authors point out that if ATMPs are to be brought to market their price will be very much higher than the cost of goods in order to cover R&D costs, translational research and in order to provide a profit to the pharmaceutical company so that they can survive and grow. By reducing manufacturing costs, the final price tag can reach a much more affordable level. If treatment developers fail to set a price that will cover their incurred expenses the product will never survive the open market. But at the same time offering ATMPs as highly overpriced products will not help them achieve commercial stability as they will not experience sufficient market penetration. An ATMP may not be seen to meet an unmet clinical need or its benefits might not outweigh its costs. This is where the question of a whether it is a curative treatment becomes important. The repudiation of current treatment costs provides one of the best arguments for a very high treatment cost for ATMPs however it is seen that streamlining the production process can reduce costs and hence the price of these novel treatments.

Regulation and marketing authorization

Bubela et al (2015) [6] make the point that the current array of small molecule pharmaceuticals only provide marginal benefits and that the cost of failure makes them expensive. They go on to claim that ATMPs present an opportunity for curative treatment 'for indications with limited treatment options'. High cost ATMPs are driven by higher R & D costs, higher manufacturing costs, the personalized nature of the product and higher clinical delivery costs. Further 'due to the likely high cost of these therapies, QALY gains must be substantial to justify the expenditure'. However, when regenerative medicine products first come to market there is likely to be quite limited evidence on clinical effectiveness. Regulatory agencies are experimenting with adaptive clinical trial designs and this will further limit the amount of clinical evidence available through small clinical trial size, use of surrogate outcomes and short duration trials. Payers then need to extrapolate long term health benefits from short duration trials, and this is difficult for therapies that are considered to be curative. As a result of small-scale short-term clinical trials and that they are insufficient to provide evidence on the curative nature of these products conditional market authorization has come to the fore. There are four conditions of approval: (1) that there is a positive benefit to risk assessment, (2) that it is likely that comprehensive clinical data will be provided, (3) that an unmet clinical need will be met, and (4) that the benefit to public health of immediate availability outweighs the risks of moving forward in the absence of additional data that would normally be required. To be effective, conditional approval mechanisms must be supported by post-market surveillance whereby regulators have the capacity and power to remove products from the market. Finally, they make the claim that there will be a reduced cost of making the wrong decision if changes are seen in the upfront cost of the technology. They propose that reimbursement is linked to performance, or the provision of additional data which would reduce the uncertainty about the value of reimbursement.

Denoon (2010) [7] commented on what is known as the 'patent cliff' and how big Pharma can ameliorate its effect by investing in ATMPs. There was a very high number of patents expiring in 2011/12 and had detrimental effect on the financial performance of pharmaceutical companies. There is strong demand for ATMPs from patient groups because many of the conditions that ATMPs currently aim to treat are orphan diseases or diseases that cannot be cured with conventional small molecule-based medicinal products. The authors suggest that ATMP products are an attractive commercial proposition to pharmaceutical companies given the pressures they face.

Denoon (2010) [7] argued that ATMPs could significantly add to economic growth if products are successfully commercialized. Relatively few ATMPs have been successfully commercialized and this is due to issues such as barriers in funding and regulatory hurdles. They suggest that translational government funding, a change in NHS and NICE organization and policies, and regulatory clarity would all improve the prospects for the successful commercialization of these products. Barriers to successful adoption of these new technologies were noted to include 'the cost of manufacturing and production scale-up, shipping and storage, lack of funding at various stages of research and development, and difficulties with demonstrating cost-effectiveness, which lead to issues with reimbursement by healthcare providers'.

Pricing

Bach et al (2017) [8] commented on tisagenlecleucel and noted that its market price of US$475,000 'shattered oncology drug pricing norms'. They highlighted that such pricing policies should make it clear that pharmaceutical companies expect to generate many millions in revenue even when only a few patients will benefit.

Kent (2017) [9] proposed that significant innovation in pricing will be one of the key determinants of the future of ATMPs. Many ATMPs, they claim, would not have made it to the clinic were it not for seed funding from patient groups. They go on to ask whether the price afforded by companies can be fully justified and if we are getting a fair and pragmatic approach from developers that ensures prices that the market is able to bear. The incentives provided by the Orphan Drugs Act in the US and the Orphan Medicinal Products Regulations in the EU have encouraged companies to view rare disease treatments as a profitable venture. The main driver of the pricing of orphan drugs, they note, is the need to recoup substantial R&D costs from a small patient population. The main issues in terms of affordability of ATMPs therefore are to do with flexibility, in terms of 'money back guarantees, risk-sharing schemes and staging of payments to reduce the challenge to short-term budgets'.

Hampson et al (2017) [4] noted that a growing number of ATMPs cost around $1-$2 million and this asks serious questions as to the sustainability of health care budgets. Long term savings in terms of alternative treatments should be considered in affordability calculations, they argue. Kent (2017) [9] highlight the example of Glybera for the treatment of lipoprotein lipase deficiency, which has been priced at US$50,000 per vial with 19 vials needed for successful treatment for the average patient. There exists 6-year follow up data showing a

50% reduction in pancreatitis in Glybera-treated patients. So dividing the up-front price with 6 years 'you get to a per-year price that's actually lower than (typical) orphan drug pricing'.

Morrison (2017) [10] refer to 3 main themes in pricing gene therapies: the classic up-front one-time payment, the annuity model that spreads payment over number of years and the pay-for-performance risk sharing model. Which one to use will depend on 'the specific attributes of any one therapy and specific negotiations between drug manufacturers and payers'. They cite Bluebird chief operating officer, Jeff Walsh "Ultimately where industry needs to go is pay for performance". For this to happen we need 'transformative data' with endpoints that can be measured and have direct correlation with disease. Spreading the cost of therapy might be more important for health insurance providers. This is because private insurance providers may only have the patient for a limited time and so they would be reluctant to pay the total cost.

Drummond and Towse (2019) [11] ask if the rate of return pricing technique is more appropriate than value-based pricing. They say that the pricing of new therapies is based on how the economic surplus generated is shared between the producer and the consumer of the therapy. In theory this is determined by the laws of supply and demand. However, in reality, payers act on the behalf of consumers and developers of technologies have patent protection and so the price has to be agreed between the two parties. Value-based pricing involves the maximum price the therapy can gain while still coming in below the willingness-to-pay threshold set by NICE. The authors claim that value-based pricing might be inappropriate when assessing ultra-rare diseases. They suggest a novel approach to pricing, that of 'rate of return' pricing. This is based on 'ensuring a pre-specified rate of return to manufacturers, after covering the costs of developing and marketing the product.' A price based on the rate of return would most probably be lower than that obtained using value-based pricing, they claim, and can be seen as the minimum price that society is willing to pay.

Health Technology Assessment

Hampson et al (2017) [4] identified three areas of challenges; evidence generation, assessing value and affordability. They note that developers of therapies targeting ultra-rare conditions may find it difficult to recruit enough patients into the trial, and it may be difficult to find an appropriate comparator. For some therapies, there may not be an easily measured patient-centred outcome so that surrogate outcomes must be used. These challenges around evidence generation makes assessing value difficult. The question arises whether additional

value should be placed on potentially curative treatments compared with more incremental benefits. Another consideration is whether small patient numbers mean that manufacturers seek prices above the cost per QALY estimates in order to make an adequate return on investment.

Bach et al (2017) [8] commented on the methodology of economic evaluation of ATMPs and state that comparisons to high cost alternatives, and thus showing a favourable incremental cost effectiveness ratio, can be misleading. Novartis, the manufacturers of tisagenlecleucel, has made plans to enter into outcomes-based contracts where the company would only be paid if the treatment was effective. This is a step towards value pricing with the potential to link the price of a treatment to the magnitude of benefit it provides. Other strategies include only charging patients who are disease free after 3 months or those with no residual disease at 30 days. By choosing proximal outcomes in this way the firm minimizes the complex administrative and financing requirements inherent to them. Possibly, it is said, a more important point than choosing the right endpoint is 'starting at the right price in the first place'. Novartis has also announced that their pricing strategy will be different for these treatments and propose what is called 'indication specific' pricing. This means that the same treatment will have more than one price in the marketplace and is a further example of value-based pricing. The authors suggest that the next generation of CAR T-cell therapies will demand a lower price because efficacy will be lower and market size larger.

Market access

Driscoll (2017) [12] claimed that current system that payers operate is not designed to absorb high cost treatments. Developers of ATMPs focus on the demands of regulators rather than payers and engage in clinical trials to prove effectiveness so that treatments can be approved by the regulators. However, it is not guaranteed that an approved treatment will become a reimbursed treatment. There are several products that are proof of this including Glybera, Provenge, ChondroCelect and MACI. According to the authors 'it is critical to take a macroeconomic view early in cell therapy product development to ensure broad market access, long-term market viability, and the possible opportunity for global implementation for new "high tech, high cost" products.' It is true that, as in the US, in Europe there has been a shift in assessing reimbursed pricing towards value-based models. Driscoll (2017) [12] point towards the lack of long-term data to assess the effectiveness of ATMPs and suggest one way to deal with this is performance-based pricing arrangements. As reimbursement frameworks differ across individual European countries, 'manufacturers need to engage with European

payers prior to embarking on pivotal trials, so that payer evidence requirements can be met at launch and patients access and revenue generation can be secured without delay'.

Hanna et al (2018) [13] highlighted the issue that there needs to be a balance between ensuring patient access to breakthrough therapies and the sustainability of the healthcare system. This is an important point. However, the 'existing traditional funding and pricing models may be insufficient to ensure the sustainability of the healthcare system'. They suggest an 'ATMP-specific fund' which may be akin to the Cancer Drugs Fund in England. In this model, funding sources would be tax-based. This fund would be based on three funding models: financial agreement, health outcomes based and healthcoin. The first, financial agreement covered discounts, rebates, price and volume caps, price-volume agreements, loans, cost-plus price, intellectual-based payment and fund-based payment. The second funding model, health outcomes were divided into performance-based payment and coverage with evidence development. Finally, healthcoin referred to a tradeable currency used to assign monetary value to incremental outcomes.

Mahalatchimy (2017) [14] claim that the main problems regarding regenerative medicine reimbursement is the high cost and low evidence of long-term cost effectiveness. However, this is not unique to regenerative medicine and parallels can be drawn with orphan drugs and their reimbursement. The lack of commercial viability due to small patient numbers has been an issue in orphan drugs and this is also an issue that faces ATMPs. A potential solution, they argue, is risk-sharing agreements. The risk is shared between the producer and the payer with a reimbursement set-up that is paid annually according to the performance of the product.

Senior (2018) [15] writes about the 'inherent difficulties in measuring cost effectiveness' which is based on big gaps in long-term efficacy and effectiveness data. The big paradox is that trials are small, uncontrolled and have relatively short follow up periods while the prices of ATMP are predicated on their long-term duration of effect. This is an issue the industry must deal with if there is to be successful commercialization of these products. As an example, they consider Yescarta relative to existing chemotherapy. According to Senior (2018) [15], if their benefit lasts only a year, they will cost $1.2 million and $5.1 million more, respectively, per QALY generated than chemotherapy. If benefits persist an average lifetime that cost per QALY shrinks to a very reasonable $57,093 per QALY for Kymriah and $145,158 for Yescarta, still within the bounds of ICER's unofficial cost effectiveness margin. Senior (2018) [15] also give real world examples of payment arrangements such as pay-for-performance using the example of Spark Therapeutics which have been in discussions with the Centers for Medicare

and Medicaid Services as to payments by instalments over several years. This is evidence of the theoretical approach to reimbursement being played out in a real-world setting.

It is noted in Touchot (2017) [16] that, at the time of writing, three gene therapies had been approved in Europe: Glybera, Imlyic and Strimvelis. Glybera had been formally evaluated through Health Technology Assessment in Germany and in France but failed to achieve a recognition of benefit in either country. As a result, the benefits of Glybera were deemed to be insufficient to justify reimbursement. The example of Glybera clearly indicates that ATMPs will be evaluated exactly like other therapies. The same criteria and scrutiny will prevail even though these therapies can only be offered to a limited number of patients. It is true that 'failure to provide respective data is likely to lead either to limited or reduced levels of reimbursement, if not to rejection of reimbursement'. However, the authors point to Strimvelis as a success story, illustrating the quality of the clinical development and the strength of the data based on long-term survival. This de-risking of the value to payers is seen as one of the reasons its commercialization was such a success.

In terms of market access it is worth noting that for Zolgensma, the manufacturers previously proposed that parents of 100 children with the disease spinal muscular atrophy should be entered into a monthly lottery in order to gain treatment at no cost, even though the actual price is $2.1 million. This approach was heavily criticized for being unethical, placing too much emotional pressure on families, and for making "SMA babies compete with each other for a life-saving treatment, splitting tightly knit communities and turning this into a coveted prize."

Reimbursement

Hampson et al (2017) [4] offered several possible solutions for the reimbursement of ATMPs. Discounts and revenue caps, for instance, are designed to limit the price of products or to set a cap within the payers' ability to pay. Another way is to target the highest value patient groups or those that are likely to achieve the highest gain from the treatments. Risk-sharing and outcomes-based payments are also suggested. These are agreements that offer money back if certain outcomes are not achieved so the risk is shared between the payer and the manufacturer. Reinsurance is another option whereby insurers seek insurance of their own to cover catastrophic pay-outs. And finally, amortization is suggested in terms of a mortgage style payment arrangement where payments are spread over a period of time thereby allowing payers to fund the treatments whilst balancing their budgets within a single year.

Bach (2018) [17] argued that implementing a single coverage policy for CAR-T therapy across Medicare in the US would 'level the financial playing field' for competing plans and ensure equal access to the therapy. Bach (2018) [17] suggested a payment approach for CAR-T therapy that promotes competition based on price. This, he claims, would be an improvement over the current system which provides hospitals with large profits when treatment costs more. If it could be shown that the net benefits of various CAR-T therapies were similar, then this would promote price competition. Another thing that would promote price competition would be by consolidating billing into a single cost code. This would have the effect of yielding the highest profit to the prescriber prescribing the lowest cost therapy and then manufacturers would 'strive to undercut one another'. Finally, it is seen that requiring a lump-sum payment forces the provider to take financial responsibility for the total cost of the therapy. If the total cost of care is less than the lump-sum amount the provider's profit will increase thus creating an incentive to choose the therapy with the least overall cost. This, in turn, incentivizes manufacturers to lower their prices.

Brennan (2014) [18] suggested a pay-for-performance model as an alternative approach to a high, single payment. It is posited that value is captured through annuity payments that are to be paid over a predetermined period and are dependent on the treatment being effective. This is therefore a type of outcomes-based payment whereby payments are effectively amortized over time rather than being an initial lump-sum. Brennan (2014) compared ATMPs with orphan drugs. In their case 'value was realized through repeated administration of medication over the life of the patient' and so with regular administration of repeated doses, together with a reasonably high price, it was possible to make a business case. ATMPs, on the other hand, potentially only require one administration. The dilemma of reimbursement could be solved by eliminating the 'perverse incentive' to prioritize investment in a repeatedly administered drug with all its associated costs to individuals and the health system, and instead investing in a one-off therapy.

Following reforms in the US healthcare system this pay-as-you-go model seems to me more workable. In terms of a one-off high price it is argued that this may encourage market failure as 'no one insurer would want to be the first to cover the medication for fear of adverse selection; that is, all the patients with a particular illness seeking policies from the one insurer providing coverage, thereby driving up costs for that insurer.' An outcomes-based pay-for-performance model would mean that the companies selling the products would participate in true risk sharing.

Ginty et al (2010) [19] corroborate the claim that achieving reimbursement is harder than gaining approval. The mechanisms of reimbursement are seen to be a 'black box' especially to those outside the US. The reimbursement potential of ATMPs, they state, must be maximized if the developing firm is to achieve a return on its significant investment in developing ATMPs. In the UK it is argued that ATMPs that present high up-front costs but give greater long-term benefits may be hard to quantify using the QALY approach because these benefits are dependent on age, life context and life responsibilities. The fact that, as is often the case, long term data are not available limits or prevents reimbursement of these therapies as a result of the high cost of development and manufacture. In the US, by contrast, reimbursement is driven by coverage and payment. Coverage is 'the treatable conditions and limitations of use established by a payer for medically necessary applications of regenerative products'. Payment is how much the payer is willing to pay for the treatment. Achieving approval is only the first step in getting a product to market. It may be the case that an approved treatment does not fall within a covered benefit and hence may not be reimbursed. However, Ginty et al (2010) [19] claim that the environment in the US is generally seen to be conducive to ATMP reimbursement. Notwithstanding that the level of data required for demonstration of product effectiveness, as opposed to efficacy, is substantial, they suggest that early dialogue between developers and payers is crucial to achieving reimbursement.

Malik et al (2014) [20] propose the '5-C' framework which is a 'structured approach to the reimbursement and adoption of advanced therapies'. It reiterates a recurring theme in these papers, that of commercial success of approved products being elusive if reimbursement is not achieved. The first reimbursement challenge that ATMPs face, claim Malik et al (2014) [20], is the high up-front cost. The second is that their positive impact on society must be recognized in cost-effectiveness analyses. A large part of the value of ATMPs are societal in nature and include benefits such as patients and carers returning to work etc. This wider aspect is often not measured in the calculation of value. Indeed value-based assessment will go a long way to address this issue and will seek to incorporate wider societal value in the assessment of ATMPs. The 5 Cs in the Asklepian model are: clinical and economic data collection, commercial launch pre-warning, clinical and economic assessment, commissioning and clinician and health facility adoption. These steps can help commercial companies achieve success in gaining reimbursement and adoption of their products.

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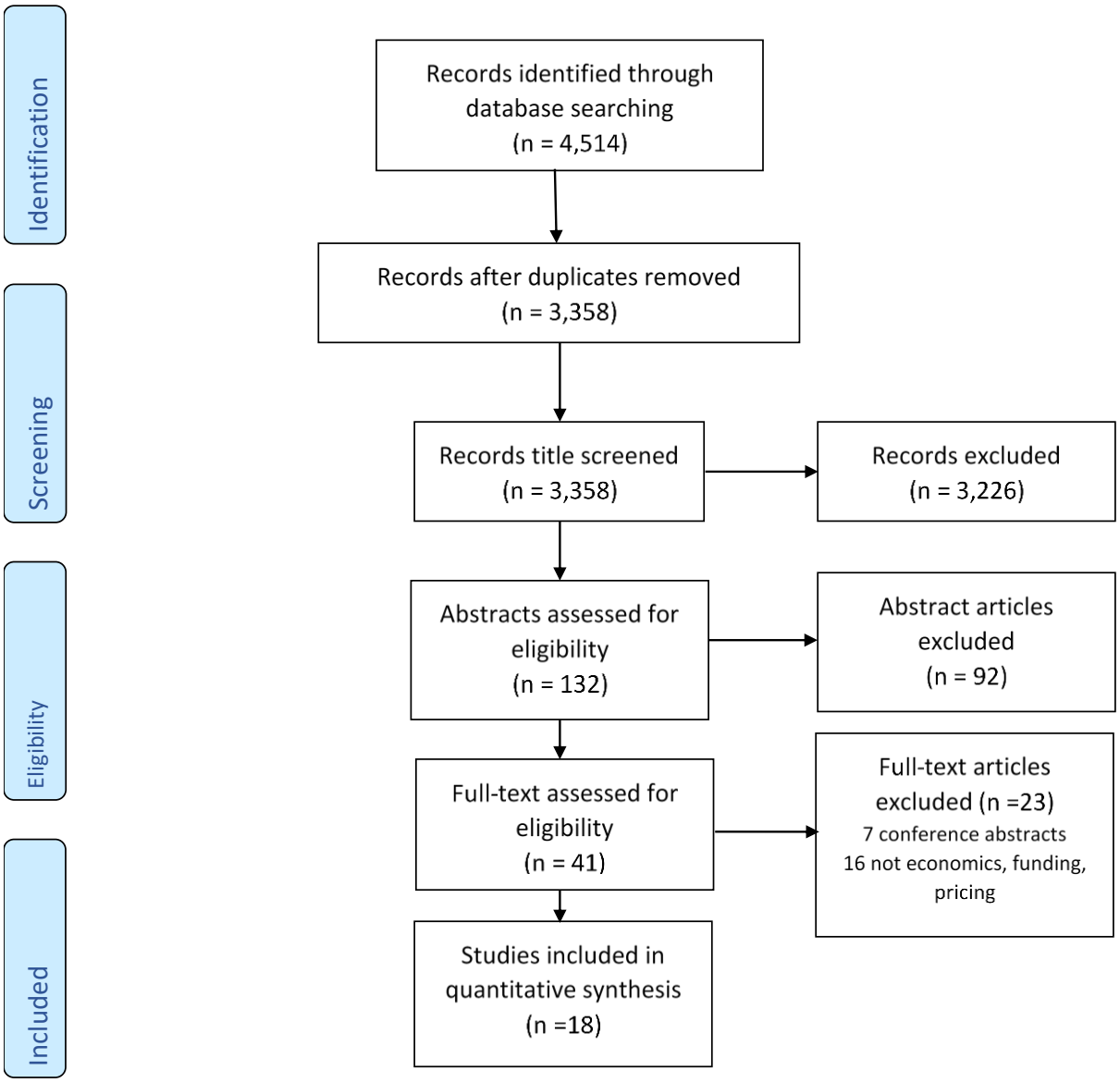

Figure 1: PRISMA flowchart for this review

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