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Systematic Literature Review

## Challenges for Economic Evaluations of Advanced Therapy Medicinal Products: A Systematic Review



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### ABSTRACT

**Objectives:** Advanced therapy medicinal products (ATMPs) are drugs for human use for the treatment of chronic, degenerative, or life-threatening diseases that are based on genes, tissues, or cells. This article aimed to identify and critically review published economic analyses of ATMPs.

**Methods:** A systematic review of economic analyses of ATMPs was undertaken. Study characteristics, design, sources of data, resources and unit costs, modeling and extrapolation methods, study results, and sensitivity analyses were assessed.

**Results:** A total of 46 economic analyses of ATMP (from 45 articles) were included; 4 were cell therapy medicinal products, 33 gene therapy medicinal products, and 9 tissue-engineered products. 30 therapies had commercial marketing approval; 39 studies were cost-utility analysis, 5 were cost-effectiveness analysis, and 2 were cost only studies. Four studies predicted that the ATMP offered a step change in the management of the condition and 10 studies estimated that the ATMP would offer a lower mean cost.

**Conclusions:** Comparison with historical controls, pooling of data, and use of techniques such as mixture cure fraction models should be used cautiously. Sensitivity analyses should be used across a plausible range of prices. Clinical studies need to be designed to align with health technology assessment requirements, including generic quality of life, and payers should aim for clarity of criteria. Regulators and national payers should aim for compatibility of registers to allow interchange of data. Given the increasing reliance on industry-funded economic analyses, careful critical review is recommended.

**Keywords:** advanced therapies, cost-effectiveness analysis, health technology assessment.

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### Introduction

Advanced therapy medicinal products (ATMPs) are drugs for human use for the treatment of chronic, degenerative, or life-threatening diseases that are based on genes, tissues, or cells.<sup>1</sup> There are currently > 2500 active clinical trials of ATMP, of those 250 are phase III.<sup>2</sup> More than 50% of these are for treatments of cancer, although investigation is underway in almost all clinical specialties.<sup>2</sup> Many ATMPs are for very specific, rare, or highly debilitating conditions and have curative intent, but others have much wider application, such as treatments for repair of knee cartilage or stress urinary incontinence.

Given the number of ATMPs under development, health service planners are concerned that new innovations offer sufficient evidence of benefits for patients at an acceptable cost. In many countries, economic evaluation is therefore an important instrument in the health technology assessment (HTA) toolkit, alongside other types of evidence (systematic review, consultation, patient perception, and so on).<sup>3</sup>

This article systematically reviews the economic evidence associated with ATMPs for the treatment of different pathologies across multiple countries. Authors sometimes claim that their study “demonstrates” that a therapy is cost-effective or not but no universal threshold can be applied.<sup>4</sup> Moreover, wider judgments often come into play, and national decision-making bodies have indicated that they may be willing to apply higher thresholds for therapies that address specific circumstances, such as unmet need or disabling diseases. For example, England conventionally applies a threshold of GBP 20 000 to 30 000 per quality-adjusted life-year (QALY),<sup>5</sup> although it has indicated that it may apply a higher threshold where certain criteria are met<sup>3</sup> and up to GBP 100 000 per QALY for highly specialized technologies, where the patient population is very small and the condition is chronic and severely disabling, among other criteria.<sup>6</sup> Nevertheless, not all countries have explicitly stated their thresholds, if they use any. In this study, thresholds of GBP 20 000, 50 000, and 100 000 per QALY are shown, corresponding to US \$28 571, \$71 429, and \$142 857. We use these thresholds for comparative and illustrative purposes

only and do not make any statement about what the appropriate threshold should be.

Previous systematic reviews have been published in some of these areas. Some specifically addressed economic evaluations of chimeric antigen receptor (CAR) T-cell therapies<sup>7-9</sup> or gene therapies.<sup>10,11</sup> Other reviews assessed the procedures and criteria used by certain US or European HTA bodies to assess ATMPs.<sup>12,13</sup> Lloyd-Williams conducted a systematic review covering economic evaluations of all types of ATMPs. These articles identified 5 broad challenges associated with the evidence underpinning ATMPs: the size and design of trials, understanding disease progression and long-term effects, estimating efficacy and comparative effectiveness, estimating impact on health-related quality of life (QOL), and generalizability. Besides effectiveness and cost-effectiveness, HTA agencies also paid attention to novel mechanisms of action, health disparities,<sup>12</sup> financing mechanisms, and social, ethical, and legal dimensions.<sup>13</sup>

In this article, we build on previous work in the following ways. The search strategy used by Lloyd-Williams was limited to mainly commercial names of gene therapy medicinal products (GTMPs) and so omitted several ATMPs derived from the use of cell therapy medicinal products (CTMPs) or tissue-engineered products (TEPs) (see definitions Appendix 1 in Supplementary Materials 1 found at <https://doi.org/10.1016/j.jval.2022.07.004>). We perform a complete systematic review by including not only commercial ATMPs but also other ATMPs under development. Where we find several models for a particular therapy and indication, we are able to compare evidence and methodology. In the specific cases where different authors have based their models around the same clinical data sources, we can pinpoint how methodological choices influence the results. This approach enables us to examine in greater detail how authors addressed the 5 broad challenges identified by Lloyd-Williams. Thus, this article aimed to identify and critically review the published economic analyses and costing studies of ATMPs to understand their strengths and weaknesses and draw out the implications for HTA for adoption, pricing, and reimbursement by health services.

## Methods

### Search Strategy

A systematic review was conducted on September 11, 2020. The searches were validated by a specialized librarian in public health and adapted for PubMed, Embase, Web of Science, Google Scholar, and The Cochrane Library (see Supplemental Material Annexes 1-3 for search terms in Appendix 2 in Supplementary Materials 2 found at <https://doi.org/10.1016/j.jval.2022.07.004>). Our search strategy includes commercial names and International Nonproprietary Names of ATMPs with marketing authorization in United States, Europe, Japan, or South Korea (main market drivers) and “tissue-engineered,” “somatic-cell therapy,” and “gene therapy” as general terms.

The grey literature search included economic analyses published by the Institute for Clinical and Economic Review group, the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Agency, and Grupo de Evaluación de Novedades, Estandarización e Investigación en Selección de Medicamentos (GENESIS), a Spanish HTA agency. The protocol was registered in the International Prospective Register of Systematic Reviews (CRD42021233727). The reference lists of the reviews and identified articles were examined, and colleagues and experts active in the field were also consulted, including suggestions by reviewers of this article.

### Study Selection and Data Extraction

Articles that conducted an economic analysis (cost, cost-effectiveness, or cost-utility analysis) of ATMPs were included. The search was limited to a period of 15 years (2005-2020). The results of the literature search were stored in a Rayyan Qatar Computing Research Institute library, and the screening process was performed in pairs, first by title and abstract (D.E. and A.O.L.), and subsequently the full-text articles were reviewed for eligibility. Differences were discussed and resolved by consensus among all authors. Articles published in a language other than English or Spanish, duplicates, congress communications, and nonsystematic reviews were excluded. No a priori exclusion criteria were applied with respect to the quality of the studies because the risk of bias associated with the study was one of the variables that we wished to analyze. Data were extracted using a template that was previously piloted, discussed, and modified by the authors.<sup>14</sup> Key information included study characteristics, study design, sources for identifying resource use, unit costs and utilities, sources of effectiveness data in the intervention and comparator groups, modeling and extrapolation methods, main study results, and sensitivity analyses.

### Risk of Bias

We evaluated the methodological quality and risk of bias of each article, using a checklist (Appendix Table S1 in Supplementary Materials 3 found at <https://doi.org/10.1016/j.jval.2022.07.004>) based on guidelines for systematic review of economic evaluations<sup>15,16</sup> and graded using the Oxford Centre for Evidence-Based Medicine scale.<sup>17</sup> Any discrepancies were discussed and agreed by consensus.

### Data Analysis

Costs and incremental cost-utility ratio (ICUR) were updated to 2020 prices<sup>18</sup> and converted from local currency to international dollars at 2020 purchasing power parity (\$1 = GBPO.70 = €0.706). The choice of the international dollar as common currency is simply for convenience.<sup>19</sup>

Some reports publish the ICUR but for confidentiality reasons do not report the incremental cost and incremental QALY.<sup>20-22</sup> Although the ICUR informs an assessment of the efficiency of the intervention, we also wished to know whether the innovation was estimated to offer a step change in the management of the disease or just a moderate added benefit and to obtain a visual overview of the incremental costs and benefits on the cost-QALY plane (see Appendix Figs. S1, S2 and S3 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). In these cases, we assumed that the incremental QALY could be appropriately proxied by that reported in another study for the same indication using similar methods for the same ATMP-comparator pair (see Methods and notes to Table 1<sup>23-45</sup>). Hence, the incremental cost associated with that ATMP-comparator pair could be back-calculated as the proxy incremental QALY multiplied by the ICUR reported in the study.

The authors worked together to elaborate recommendations for HTA evidence, procedure, and criteria of relevance for ATMP, based on the evidence extracted from the review. Nevertheless, all conclusions are exclusively those of the authors.

## Results

### Selection of Included Studies

A total of 1522 articles were assessed for eligibility (Appendix Fig. S4 in Supplementary Materials 5 found at <https://doi.org/10.1016/j.jval.2022.07.004>). After excluding those articles not related

**Table 1.** Treatment comparisons evaluated within a cost-utility analysis.

Therapy	Comparator	Incremental cost (\$)	Incremental QALY	ICUR
<b>Therapies that offer lower QALY than the current SOC</b>				
Stress urinary incontinence (TEP)				
VilSBøll et al, 2018 <sup>24</sup>	MM vs MUS	−806	−0.058	13 966
VilSBøll et al, 2018 <sup>24</sup>	IVM vs MUS	440	−0.008	Dominated
<b>Therapies that may offer a major improvement in the management of the condition with considerably greater cost</b>				
Adenosine deaminase deficiency (GTMP)				
South et al, 2018 <sup>58</sup>	Strimvelis vs HSCT MUD	951 936	8.5	111 992
Spinal muscular atrophy (GTMP)				
Ellis et al, 2019 <sup>36</sup>	Nusinersen vs SOC	3 095 000	2.78	1 113 309
Ellis et al, 2019 <sup>36</sup>	Zolgensma vs SOC	2 868 000	11.77	243 670
Malone et al, 2019 <sup>29</sup>	Zolgensma vs nusinersen	−2 175 846	10.36	Dominates
Relapsed/refractory B-ALL (GTMP)				
Ribera Santasusana et al, 2020 <sup>32</sup>	Kymriah vs SOC	264 347	8.97	29 470
Thielen et al, 2020 <sup>37</sup>	Kymriah vs Blinatumab	567 877	10.84	52 729
SMC 2019a <sup>21*</sup>	Kymriah vs SOC	Confidential	Confidential	36 054
Walton 2018 <sup>20*</sup>	Kymriah vs SOC	Confidential	Confidential	43 493
Whittington et al, 2019 <sup>53</sup>	Kymriah vs SOC	341 020	7.18	47 496
Lin et al, 2018 <sup>31</sup>	Kymriah vs SOC	328 085	5.17	63 459
Sarkar et al, 2018 <sup>52</sup>	Kymriah vs SOC	558 259	8.18	68 247
Furzer et al, 2020 <sup>60</sup>	Kymriah vs SOC	357 020	6.79	141 000
Hettle et al, 2017 <sup>34</sup>	CAR T vs SOC (bridge to HSCT)	565 404	7.46	75 791
Hettle et al, 2017 <sup>34</sup>	CAR T vs SOC (curative intent)	762 511	10.07	75 721
Relapsed or refractory DLBCL (GTMP)				
SMC 2019a <sup>21†</sup>	Kymriah vs SOC	Confidential	Confidential	71 393
Lin et al, 2019 <sup>42</sup>	Kymriah vs SOC	368 316	2.14	172 110
Cher et al, 2020 <sup>30</sup>	Kymriah vs SOC	264 354	0.508	520 381
Roth et al, 2018 <sup>27</sup>	Yescarta vs SOC	393 478	6.54	60 165
SMC 2019b <sup>22</sup>	Yescarta vs SOC	287 797	4.1	70 194
Whittington et al, 2019 <sup>53</sup>	Yescarta vs SOC	351 100	1.89	230 900
Lin et al, 2019 <sup>42</sup>	Yescarta vs SOC	493 134	3.72	132 563
Tice 2019 <sup>59</sup>	Yescarta vs SOC	478 200	3.39	141 062
Corbett et al, 2018b <sup>39</sup>	Yescarta vs SOC	Confidential	Confidential	N/A
<b>Therapies that offer some (or uncertain) additional health benefit with greater (or uncertain) total mean cost</b>				
BCG-unresponsive non-muscle invasive bladder cancer (GTMP)				
Altas et al, 2020 <sup>40</sup>	Nadofaragene Fir. Vs hypothetical comparator	119 000	0.79	150 633
Biallelic RPE65-mediated retinal disease (GTMP)				
Banken et al, 2018 <sup>43</sup>	Luxturna vs SOC	854 490	1.3	657 300
Uhrmann et al, 2020 <sup>45</sup>	Luxturna vs SOC	32 542	4.82	156 853
Viriato et al, 2020 <sup>44</sup>	Luxturna vs SOC	612 404	6.4	95 072
Johnson 2019 <sup>68†</sup>	Luxturna vs SOC	−104 610	9.4	Dominates
Cartilage defect in knee (TEP)				
Samuelson et al, 2012 <sup>28</sup>	ACI-C vs ACI-P	−1071	0.07	Dominates
Clar et al, 2005 <sup>23</sup>	ACI vs MF	3805	0.564	6746
Clar et al, 2005 <sup>23</sup>	MACI vs MF	N/A	N/A	N/A
Mistry et al, 2017 <sup>35</sup>	ACI vs MF	22 168	0.994	22 292
Gerlier et al, 2010 <sup>33</sup>	CC vs MF	34 745	1.282	27 102
de Windt et al, 2016 <sup>46</sup>	CC vs MF	36 330	0.04	908 251
de Windt et al, 2016 <sup>46</sup>	IMPACT vs MF	8777	0.04	219 424
<b>Asymptomatic metastatic castration-resistant prostate cancer (CTMP)</b>				
Gong et al, 2014 <sup>61</sup>	Sipuleucel-T vs prednisone	94 411	0.16	547 298
<b>Therapies that offer some additional health benefit with lower total mean cost</b>				
Advanced metastatic melanoma (GTMP)				
Retèl et al, 2018 <sup>26</sup>	TIL vs Ipilimumab	−19 886	0.07	Dominates
Dopamine cell therapy for Parkinson disease (C)				
Hjelmgren et al, 2005 <sup>63</sup>	Cell therapy vs SOC	−47 415	1.133	Dominates
Hemophilia A (GTMP)				
Rind et al, 2020 <sup>41</sup>	Valoctocogene rox. vs FVIII	−5 029 000	0.004	Dominates
Cook et al, 2020 <sup>62</sup>	Valoctocogene rox. vs FVIII	−6 810 374	0.750	Dominates
Machin et al, 2020 <sup>49</sup>	Gene Tx vs FVIII	−716 170	1.71	Dominates
Ischemic stroke (CTMP)				
Svensson et al, 2012 <sup>25</sup>	Stem cell therapy vs SOC	−22 336	1.34	Dominates

ACI indicates autologous chondrocyte implantation; B-ALL, B cells acute lymphoblastic leukemia; BCG, Bacille Calmette-Guérin; CAR T, chimeric antigen receptor T-cell therapy; C, I/III collagen patch; CC, ChondroCelect; CTMP, cell therapy medicinal product; DLBCL, diffuse large B-cell cell lymphoma; FVIII, factor VIII; GTMP, gene therapy medicinal product; HSCT, hematopoietic stem cell transplant; ICUR, incremental cost utility ratio; IMPACT, Instant MSC Product Accompanying ACI; IVM, in vitro expanded myoblasts; MACI, matrix-guided autologous chondrocyte implantation; MF, microfracture; MM, minced myofibers; MUD, matched unrelated donor; MUS, midurethral sling; N/A, not applicable; P, periosteal patch; QALY, quality-adjusted life-year; rox., roxaparfovec; RPE, retinal pigment epithelium; SOC, standard of care; SMC Scottish Medicines Consortium; TEP, tissue-engineered product; TIL, tumor infiltrating lymphocyte; Tx, therapy.

\*Incremental QALY or cost not reported. It was assumed for the graphs that the incremental QALY would be the same as that reported in Lin et al, 2019.<sup>42</sup>

†Incremental QALY or cost not reported. It was assumed for the graphs that the incremental QALY would be the same as that reported in Whittington et al, 2019.<sup>53</sup>

‡Johnson 2019 (reference 64) estimates lower cost and greater QALY for the intervention compared with standard of care.

**Table 2.** Characteristics of the included articles (N = 46).

Pathology	n = 3	n = 31	n = 9	N = 46	100%
	CTMPs	GTMPs	TEPs	Total	%
R/R DLBCL	-	9	-	9	20
R/R B-ALL	-	9	-	9	20
Cartilage defects in knee joints	-	0	7	7	15
Hemophilia A	-	3	-	2	4
Spinal muscular atrophy	-	2	-	2	4
RPE65-mediated inherited retinal degeneration	-	4	-	4	8
Other	3	8	2	13	28
Source of human cells	CTMPs	GTMPs	TEPs	Total	%
Allogeneic	2	1	1	4	9
Autologous	2	32	8	42	91
Therapies with MA (commercial name)	CTMPs	GTMPs	TEPs	Total (N = 31)	%
Alofisel	1	-	-	1	3
Chondrolect	-	-	2	2	6
Imlygic	-	1	-	1	3
Kymriah	-	12	-	12	39
Luxturna	-	4	-	4	13
MACI	-	-	1	1	3
Strimvelis	-	1	-	1	3
Yescarta	-	5	-	5	16
Yescarta & Kymriah	-	1	-	1	3
Zolgensma	-	2	-	2	6
Zynteglo	-	1	-	1	3
Therapies without MA or unspecified	CTMPs	GTMPs	TEPs	Total (N = 14)	%
ACI	-	-	3	3	21
CAR T/TIL	-	2	-	2	14
Dopamine cell replacement therapy	1	-	-	1	7
Hypothetical gene therapy	-	1	-	1	7
In vitro expanded myoblasts	-	-	1	1	7
IMPACT	-	-	1	1	7
Nadofaragene firadenovec	-	1	-	1	7
Stem cell therapy	1	-	-	1	7
Valoctocogene roxaparvovec	-	2	-	2	14
Corneal tissue-engineered constructs	-	-	1	1	7
Setting	CTMPs	GTMPs	TEPs	Total (N = 46)	%
Belgium	-	-	1	1	2
Germany	-	-	1	1	2
Canada	-	-	1	1	2
Denmark	-	-	1	1	2
France	-	1	-	1	2
The Netherlands	-	2	1	3	7
Norway	-	-	1	1	2
Singapore	-	1	1	2	4
Spain	1	1	1	3	7
Sweden	2	-	-	2	4
UK	-	1	1	2	4
UK-Scotland	-	3	-	3	7

*continued on next page*

**Table 2.** Continued

Pathology	n = 3	n = 31	n = 9	N = 46	100%
	CTMPs	GTMPs	TEPs	Total	%
UK-England	-	5	1	6	13
US	-	15	1	19	41
Type of economic evaluation	CTMPs	GTMPs	TEPs	Total	%
CEA	1	1	2	4	9
CUA	3	31	6	40	87
Costs only	0	1	1	2	4
Type of study	CTMPs	GTMPs	TEPs	Total	%
Within trial	-	1	-	1	2
Decision tree model	2	1	7	10	24
Microsimulation model	-	1	-	1	2
Markov model	1	12	2	14	34
Partitioned survival model	-	15	-	15	37
Publication year	CTMPs	GTMPs	TEPs	Total	%
2006	1	-	-	1	2
2010	-	-	1	1	2
2012	1	-	2	3	7
2014	-	-	1	1	2
2016	-	-	1	1	2
2017	-	2	1	3	7
2018	1	10	2	13	30
2019	-	2	-	9	21
2020 (Jan-Sept)	-	10	1	11	26

ACI indicates autologous chondrocyte implantation; CAR T, chimeric antigen receptor T-cell therapy; CEA, cost-effectiveness analysis; CTMP, cell therapy medicinal product; CUA, cost-utility analysis; GTMP, gene therapy medicinal product; IMPACT, Instant MSC Product Accompanying ACI; Jan, January; MA, market authorization; MACI, matrix-guided autologous chondrocyte implantation; R/R B-ALL: relapsed/refractory B-cell acute lymphoblastic leukemia; R/R DLBCL: relapsed or refractory diffuse large B-cell lymphoma; relapsed/refractory B-cell acute lymphoblastic leukemia; RPE, retinal pigment epithelium; Sept, September; TEP, tissue-engineered product; TIL, tumor infiltrating lymphocyte; UK, United Kingdom; US, United States.

with the review, duplications, and congress communications (n = 1522), 46 evaluations were selected for analysis (Appendix Table S2 in Supplementary Materials 6 found at <https://doi.org/10.1016/j.jval.2022.07.004>).<sup>20-63</sup>

A total of 4 evaluations reviewed CTMPs, 33 GTMPs, and 9 TEPs (Table 2). A total of 31 were for therapies with commercial marketing approval from the European, US, Japanese, or Korean regulators, and 14 were for therapies that do not yet have approval for the indication or are hypothetical products. 39 studies were cost-utility analysis, 5 were cost-effectiveness analysis, and 2 were cost only studies. One study was trial based,<sup>50</sup> that is, based exclusively on primary data on resource use and effectiveness, whereas all other studies were models, that is, mainly based on secondary data extracted from other studies and literature. Twenty-five articles had not been included in the previous review of economic evaluations of ATMPs.<sup>64</sup>

### Cost-Utility Analyses of ATMP

Of the 39 cost-utility analysis studies, 1<sup>39</sup> reported only methods but did not report costs, QALY, or ICUR for confidentiality reasons. Of the remaining 38 studies, 5 reported cost and QALY, for 3 treatment options (ie, 2 ATMPs plus a comparator or 1 ATMP vs 2 comparators). From this literature, we were able to obtain incremental cost and incremental QALY or ICUR estimates for 42 ATMP-

comparator pairs, listed in Table 1. These were classified in 4 broad groups, according to their base-case point estimates on the cost-QALY plane: those that offer no added benefit, those that offer a major improvement in the management of the disease at increased cost, those that offer some (or highly uncertain) added benefit at increased (or uncertain) cost, and those that offer added benefit at a lower cost.

Vilsbøll et al<sup>24</sup> concluded that neither in vitro expanded myoblasts nor minced myofibers would offer an improvement in QALY for stress urinary incontinence relative to standard of care (SOC), in this case, midurethral sling (Appendix Fig. S1 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). The other ATMPs included in this review were associated with some positive QALY gain. In the cases of Strimvelis for adenosine deaminase deficiency, Zolgensma for spinal muscular atrophy, Yescarta for relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), and Kymriah relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL), the expected point estimate of gain in QALY was large or extremely large, ranging from 3.4 years (Yescarta) to 11.7 years (Zolgensma). HTA agencies have stated that expected gains in the upper range of this magnitude can be considered a step change in the clinical management of these diseases<sup>6</sup> (Appendix Fig. S2 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). Nevertheless, in these cases, the ATMPs were associated with a

considerable incremental cost compared with SOC, even after offsetting expected cost savings associated with reduced need for other healthcare. Yescarta for DLBCL was expected to require an additional expenditure of between \$290 000 and \$490 000 per patient, Kymriah for B-ALL an additional expenditure of between \$260 000 and \$560 000, Strimvelis an additional expenditure of almost \$1 million per patient, and Zolgensma an additional expenditure of >\$2.8 million per patient over SOC. Strimvelis was considered cost-effective by NICE as the ICUR was estimated to be <£100 000 (\$142 000)/QALY, the threshold for specialized technologies. Zolgensma was found by Malone et al<sup>29</sup> to be cost-saving compared with nusinersen (another costly innovative medicine) but Ellis et al<sup>36</sup> found an ICUR in excess of \$250 000/QALY when Zolgensma was compared with SOC.

In the cases of ATMPs to treat advanced metastatic melanoma, Bacille Calmette-Guérin unresponsive non-muscle invasive bladder cancer, biallelic retinal pigment epithelium (RPE)-65 mediated retinal disease, cartilage defects in knee joints, hemophilia A, and ischemic stroke, the expected QALY gains were smaller or greatly varying among studies (Appendix Fig. S3 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). In the case of autologous chondrocyte implantation (ACI) versus microfracture for cartilage defects in knee joints, 3 studies found the ICUR would be < £20 000 (\$28 571)/QALY whereas 1 study<sup>46</sup> found the incremental cost-effectiveness ratio would be considerably > £100 000 (\$142 000)/QALY. In four indications (advanced metastatic melanoma, haemophilia A, Parkinson's disease and ischaemic stroke) the product is associated with QALY gains and cost savings (Appendix Fig. S4 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). Hence, the ICUR would be negative and is not relevant for decision making.

### Utilities Used in the Cost-Utility Analyses

Only a few clinical trials included health-state utilities obtained from generic instruments that use preference-based weights (EQ-5D, Short Form 6-Dimension, or Health Utilities Index). Examples were the ZUMA-1<sup>65</sup> trial (Yescarta for R/R DLBCL) and the JULIET trial<sup>66</sup> (Kymriah for R/R DLBCL). One evaluation of Zolgensma and one of Luxturna elicited patient QOL from physicians.<sup>29,44</sup> The evaluation of Strimvelis assumed that treated patients would enjoy the same QOL as the general population for that age. A study of Luxturna used utility weights associated with other retinal disease populations, although it noted that these are often older patients.<sup>43</sup> Other studies used values from the literature to map from disease-specific severity instruments (such as the Rankin score for stroke severity<sup>25</sup> or oncology QOL scales<sup>31</sup> to utility scales such as the EQ-5D or Health Utilities Index).

### Sources of Clinical Evidence and Modeling Methods Used in the Cost-Utility Analyses

Data from <25 patients were available in the intervention arms for adenosine deaminase deficiency, biallelic RPE-65, hemophilia A, and spinal muscular atrophy (Table 3). The data used for the comparator group treatment ranged in duration from 1 year to 28 years of follow-up (Table 3), whereas the duration of the data for the ATMP patients was from 1 to 13 years of follow-up.

For some modeling studies, several sources of data were available, and the authors pooled those data sets. For instance, the evaluations of TEP for urinary stress incontinence pooled aggregate published data from 3 case series with between 20 and 117 patients ignoring between-study differences.<sup>24</sup> By

contrast, several evaluations of Yescarta for R/R DLBCL used the SCHOLAR-1 study to estimate survival with the comparator (salvage chemotherapy). SCHOLAR-1 pooled carefully selected individual data from 2 randomized controlled trials (RCTs) and 2 cohort studies and considered possible sources of between-study variation.<sup>67</sup>

There were also 4 economic evaluations of Luxturna, one of which estimated a small added benefit at high incremental cost,<sup>43</sup> 1 estimated a very large added benefit with cost savings,<sup>68</sup> and 2 estimated a large added benefit with additional cost.<sup>44,45</sup> All used efficacy evidence from the same small 4-year RCT.<sup>69</sup> The economic evaluations differed in various ways (discount rates, number of health states, and perspective) but 2 factors stand out. The RCT did not collect QOL variables that could be used to estimate utility. Hence, the economic studies used different sources for the utility associated with visual difficulty (studies in a different pathology or the opinion of experts). The second crucial difference was the assumption about how long the treatment benefit might last. All models affirmed that the costs of the disease increase with the severity of visual impairment, particularly the indirect (non-healthcare) costs, and so a gene therapy that could slow the progression of visual impairment would gradually offset the high acquisition cost. Nevertheless, there were no data on the duration of effectiveness of the gene therapy beyond 4 years, so the models relied on assumptions, 1 assuming the effect gradually wanes over 10 years,<sup>43</sup> 1 assuming it is maintained for 40 years,<sup>44</sup> and 2 assuming it is maintained over the lifetime.<sup>45,68</sup>

### Time Horizons Used in the Cost-Utility Analyses

Most studies (34 of 39) used mathematical models to extrapolate clinical effectiveness from trial data in the intervention and control group to longer term outcomes, using time horizons of 40 years or more. The remainder (5 of 39) used a time horizon no longer than the length of the trial data (between 1 and 9 years).

### Prices of ATMPs Used in the Cost-Utility Analyses

In some studies, the price of the ATMPs was unknown to the authors, and a “placeholder” price was used instead. For example, Malone et al<sup>29</sup> varied the price of Zolgensma from \$2.5 million to \$5 million per patient. Whittington et al<sup>53</sup> in an evaluation of Kymriah versus SOC for R/R B-ALL used a price of \$575 000 including hospital markup. Nevertheless, they assumed an outcome-based agreement where payment would only be charged for patients who respond to Kymriah treatment at 1 month. It was expected that approximately 15% of patients would be unresponsive and hence incur no therapy acquisition cost.

Three economic evaluations of ChondroCelect (a TEP) used commercial prices ranging from \$16.000 to \$20.802 depending on the national health system.<sup>33,35,56</sup> Many other studies of TEP were undertaken while the therapy was under development, before the commercial price was established, and manufacturing costs were used instead.<sup>23,24,28,46,55</sup>

The health services in England and Scotland also negotiate discounts or other reimbursement agreements with manufacturers, referred to as “Patient Access Schemes.” Corbett et al<sup>38</sup> published the ICUR estimated for Kymriah versus SOC for R/R DLBCL but did not reveal the incremental costs or QALYs. A study of Yescarta versus SOC for R/R DLBCL did not report the ICUR.<sup>39</sup> Luxturna has a list price of \$850 000 per patient.<sup>43</sup> Nevertheless, Luxturna was recommended in Germany at a reported €345 000 (\$489 000) per patient and for use in National Health Services in England at a confidential discount.<sup>70</sup>

**Table 3.** Duration and number of patients in the clinical trials used by the models to estimate comparative efficacy (N = 39).

Pathology	No. of studies	Duration of source data for control group (years)	Duration of source data for intervention group (years)	No. of patients in the intervention study arm
Adenosine deaminase deficiency	1	10	13	18
Advanced metastatic melanoma	1	1	1	51
BCG-unresponsive non-muscle invasive bladder cancer	1	N/A	N/A	N/A
Biallelic RPE65-mediated retinal disease	4	28	3-8.9	21
Cartilage defect in knee	6	3-10	3-10	51-101
Hemophilia A	3	5-10	0.5	15
Ischemic stroke	1	10	N/A	N/A
Spinal muscular atrophy	3	1	2-4	15
Stress urinary incontinence	2	1	1	20-177
Relapsed or refractory DLBCL	9	1-10	1.2-2	93-108
Relapsed/refractory B-ALL	9	1.7-3	1.7-5	N/A-75

B-ALL indicates B cells acute lymphoblastic leukemia; BCG, Bacille Calmette-Guérin; DLBCL, diffuse large B-cell cell lymphoma; N/A, these data were neither reported in the study nor were available from the reference list of the study; RPE, retinal pigment epithelium.

### Studies That Estimated Costs or Cost-Effectiveness

As shown in Table 4,<sup>48,50,51,54–57,71</sup> 1 study only estimated costs in the intervention group (not the difference in cost), and 1 estimated costs for a TEP for corneal blindness, compared with procured donor tissue. Notably, 5 estimated cost-effectiveness (ie, measures of health outcome that were not QALY), namely, patient response and patient reported measures,<sup>48,56</sup> avoidance of complications and hospital admissions,<sup>50</sup> disease remission,<sup>54</sup> and “progression-free quality-adjusted life-years.”<sup>71</sup>

### Risk of Bias

The main risks of bias (Appendix Table S3 in Supplementary Materials 7 found at <https://doi.org/10.1016/j.jval.2022.07.004>) identified were conflict of interest, lack of generalizability (unknown prices or prices based on confidential agreements), and concerns about the adequacy of evidence and modeling of treatment benefit beyond the trial data (lack of detailed resources and unit costs, insufficient time horizon, lack of data on long-term efficacy and safety, and structural modeling choices).

A common risk of bias arose from the inadequacy of the clinical evidence. Studies of Luxturna and ACI used evidence from RCTs (level 2 evidence).<sup>17</sup> The 2 studies of Yescarta compared the intervention group cohort and a historical control group after adjusting statistically for differences in the 2 cohorts (level 3 evidence). A study of cell therapy for ischemic stroke only used expert opinion (level 5 evidence), whereas all other studies compared single-arm intervention groups with historic controls without adjusting for differences in the 2 cohorts (level 4 evidence). These issues are commented on further in the discussion section.

### Discussion

In the following sections, we pinpoint in more depth how the studies in this review addressed the 5 evidentiary challenges identified by Lloyd-Williams<sup>64</sup> and discuss the implications of our findings for regulatory approval and Price & Reimbursement (P&R) of ATMPs in national health systems.

### Size and Design of Trials

As far as medicine regulators (European Medicines Agency [EMA] and Food and Drug Administration) were concerned, the key trials for Strimvelis, Luxturna, and valoctocogene roxaparvovec had very low patient numbers, but this was not necessarily a barrier to evaluation. For example, despite considerable uncertainty, regulators accepted that Strimvelis and Luxturna showed demonstrable benefit and these medicines were approved under conditional marketing approval (CMA). Likewise, these medicines obtained recommendation for use in some national health services.<sup>70</sup> Conversely, the low quality of evidence for valoctocogene roxaparvovec led to both the EMA and Food and Drug Administration (at that time) to reject marketing approval citing lack of effectiveness emerging from a preliminary analysis of a phase III study.<sup>72,73</sup> The clinical studies of Strimvelis and Luxturna had long follow-up (18 years and 3 years, respectively) of clinically relevant outcomes, providing some reassurance that therapeutic benefit would be maintained, whereas the study of valoctocogene roxaparvovec was for only 6 months and did not report bleed events. These examples show that even when there are low patient numbers, the evidence can meet decision makers' criteria for approval provided other aspects of the study design are appropriate.

Other evaluations in this review pooled clinical data across multiple small studies. This can augment precision, but must be conducted with methodological rigor. Investigating the causes of the differences between studies may be more useful than estimating some average effect by uncritically pooling primary studies.<sup>74</sup>

### Evidence on Efficacy and Comparative Effectiveness

RCTs are considered high grade evidence of the treatment effect.<sup>17</sup> Studies of Luxturna and ACI obtained treatment effects from RCTs.<sup>33,35,43,46,56</sup> Nevertheless, regulators and payers have accepted lower grade evidence for some ATMPs.<sup>34,75</sup> When RCT evidence is unavailable, it is important that analysts use appropriate methods to ensure that intervention and control groups are comparable. For example, our review includes 6 evaluations of

**Table 4.** Results of studies that estimated costs or cost-effectiveness (N = 7).

Study	Therapy vs comparator	Difference in cost, \$	Difference in effectiveness (if reported)
Relapsed or refractory DLBCL (GTMP) Yang et al <sup>51</sup>	Kymriah vs N/A	N/A	N/A
Corneal blindness due to endothelial dysfunction (TEP) Tan et al <sup>55</sup>	Tissue-engineered constructs vs procured donor tissue	-2830	N/A
Crohn's disease and fistulas (CTMP) Castañeda et al <sup>54</sup>	Alofisel vs surgery	75 561	NNT of 6 (for combined remission at 24 weeks)
Cartilage defect (TEP) Sierra et al <sup>56</sup> Aae et al <sup>48</sup>	Chondrocelect vs MF ACI vs MF	30 501 14 353	NNT of 5 (for response on KOOS scale) 7-point improvement in KOOS (0-100 scale)
β-thalassemia (GTMP) Coquerelle et al <sup>50</sup>	Zynteglo vs HSCT	575 411	No difference in survival; 3 times fewer complications than HSCT group
Melanoma (GTMP) Almutairi et al <sup>71</sup>	Imlygic/ipilimumab vs ipilimumab	362 033	0.16 progression-free quality-adjusted life-years

ACI indicates autologous chondrocyte implantation; CTMP, cell therapy medicinal product; DLBCL, diffuse large B-cell cell lymphoma; GTMP, gene therapy medicinal product; HSCT, hematopoietic stem cell transplant; KOOS: Knee injury and Osteoarthritis Outcome Score; MF, microfracture; N/A, not available; NNT, number needed to treat; TEP, tissue-engineered product.

Yescarta versus SOC for R/R DLBCL (Table 1). In these cases, the single-arm study ZUMA-1<sup>65</sup> was compared with historical controls (SCHOLAR-1).<sup>67</sup> Two studies<sup>27,39</sup> (essentially based on the same model) statistically matched the treatment and SOC cohorts and stated that the matching did not affect the results.

### Evidence and Modeling Methods Used to Describe Disease Progression and Long-Term Effects

In a model, there are often a number of options about how disease progression or overall survival can be predicted after the time horizon of the clinical study. For example, using data from the same clinical study, some of the Yescarta economic studies<sup>59</sup> measured clinical response (partial or complete) and survival conditional on response, whereas others<sup>27</sup> measured the “cure rate” using a mixture cure fraction model<sup>76</sup> and survival conditional on cure. “Response” and “cure” are not synonyms. For example, the ZUMA-1<sup>65</sup> trial estimated that 39% of patients had “ongoing response,” that is, durable remission, considerably fewer than the 50% estimated by the mixture cure model. A mixture cure model is not based on any clinical definition of a cure or information on the patient's pathology. The cure fraction is derived from a perceived “statistical” property of the survival curve, that is, the point at which survival is estimated to plateau. Hence, although it is tempting to interpret the output of the mixture cure model in clinical terms such as the proportion of patients in long-term remission or similar terms, such an interpretation is not warranted. In this case, the apparent disconnect between the clinical response rate and the modeled cure fraction was noted by the evaluation committee at NICE, but not considered to be a major limitation. Nevertheless, analysts and decision makers should be aware of these issues.

Another potentially important source of uncertainty is whether the early treatment effect might diminish (wane) over time. In the example of Yescarta, several approaches were used across the different studies, including extrapolating based on parametric functions,<sup>59</sup> assumptions based on optimistic and

pessimistic scenarios,<sup>31</sup> assumptions about minimal further risk if a patient survives 5 years without progression,<sup>31</sup> or minimal further risk for patients identified as “cured” by the mixture cure fraction model.<sup>27</sup> Lin et al<sup>42</sup> noted that industry-funded analyses<sup>27</sup> of Yescarta generally used more favorable assumptions and estimated lower ICURs than nonindustry studies.

The example of Luxturna also permits an insight into how different assumptions about waning can influence results. Extrapolating from the same short term clinical study data, studies differed in how long the gene therapy would prevent deterioration of vision. Those that assumed a longer time free of progression consequently also predicted that the acquisition cost of the therapy would be offset by savings in healthcare and costs to wider society. As with Yescarta, industry funding may have influenced authors in their choice of base-case assumptions.

### Evidence on Health-Related QOL

Although some ATMPs may aim to offer increased survival, others aim to relieve diseases that affect QOL. These data are often lacking in clinical studies. In the study of Luxturna, the main areas of uncertainty centered around mapping visual acuity to utility.<sup>43</sup> Given a lack of data in the target population, the sponsor used data from patients with another retinal condition. In this case, the NICE decision committee agreed with the sponsor that the gains in visual acuity would translate into large gains in QOL.<sup>77</sup> Other studies reached similar conclusions based on the opinion of clinical experts about patient utility.<sup>68</sup>

### Generalizability

The price of ATMPs can limit the generalizability of a study given that prices in one jurisdiction do not apply to others, or price data are confidential. By comparing reported results, we made some very approximate guesses about what these confidential prices might be. For example, in the case of Luxturna, at the list price of \$850 000 per patient, the ICUR estimated by NICE was almost GBP100 000 (\$143 000)/QALY, well in excess of the usual



**Table 5.** Main conclusions and recommendations.

Domain	Finding of the literature review	Implications for regulatory approval, HTA, pricing, and reimbursement	Recommendations
Size and design of clinical studies	Evaluations of ATMP in rare diseases often are based on studies with very few patients.	Regulators and payers have accepted small studies provided other aspects of study design are adequate.	Appropriate length of follow-up and endpoints are crucial. Sources of between-study heterogeneity must be explored.
Efficacy and clinical effectiveness	RCTs are often infeasible in indications where standard of care is ineffective.	Regulators and payers have accepted well-conducted nonrandomized study designs.	Analyses should take account of baseline differences between intervention and control groups.
Modeling disease progression and extrapolation	Clinical studies may be short term or use surrogate outcomes.	Regulators and payers are concerned that treatment effects may be temporary or not lead to measurable and clinically relevant benefits for patients.	Use of statistical models such as mixture cure fraction models should be undertaken cautiously and results compared with clinical measures of freedom from remission.
Health-related quality of life	Clinical studies often lack quality of life data.	Regulators and payers are demanding outcomes relevant for patients.	Clinical studies should include generic quality of life instruments.
Generalizability	Between-country differences in prices of ATMPs and reimbursement schemes may be threats to generalizability of economic studies.	Prices and reimbursement schemes are often confidential.	Economic evaluations should conduct sensitivity analyses and threshold analyses for a plausible range of prices.
Criteria for HTA	HTA criteria set by payers for P&R are often opaque and inconsistent.		Payers should aim for consistency and clarity. Routine HTA evidentiary requirements and criteria should apply unless there is a strong case otherwise. Manufacturers need to ensure they design clinical studies that align with HTA criteria.
Managing uncertainty	ATMP are often associated with high financial and clinical uncertainty.	Market entry is increasingly initiated using outcome-based reimbursement agreements.	There is a patchwork of post marketing surveillance platforms. Regulators and national payers should aim for compatibility and interchange of data.
Use of hospital exemption	National medicine regulatory agencies in the European community can authorize and supervise some ATMP without European Medicines Agency centralized approval.		Hospital exemption should be reviewed to ensure transparency and best interests of patients.
Risk of bias	Economic models can be highly sensitive to assumptions. In some cases, industry-funded economic studies estimated more favorable net benefit.	HTA agencies are increasingly reliant on industry dossiers to provide clinical and economic evidence.	Careful critical evaluation of industry dossiers is required, alongside comparison with non-industry-funded models where possible.

ATMP indicates advanced therapy medicinal product; HTA, health technology assessment; P&R, Price & Reimbursement; RCT, randomized controlled trial.

reference threshold.<sup>44</sup> Nevertheless, Luxturna was recommended in Germany at a reported discounted price of €345 000 (\$489 000) per patient,<sup>70</sup> and although the discount in England was confidential, a similar price to Germany would bring the ICUR much closer toward NICE's usual threshold.<sup>44</sup>

### Criteria for HTA for Adoption Into Health Services

There has been debate about whether ATMP should be evaluated (or priced or reimbursed) using different criteria to other therapies.<sup>78</sup> Some gene therapies potentially could produce

lifelong benefits, but with high financial risk (a one-off treatment with uncertain outcome) and considerable evidentiary uncertainty (difficulty of conducting RCTs in rare diseases with no effective alternative therapies). Some of the medicines in this review have these properties. Strimvelis, Zolgensma, and chimeric antigen receptor T-cell therapy (CAR T) are in the top-right quadrant (Appendix Fig. S2 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>) and could be considered to offer a step change in clinical management, but they are also among the medicines with the highest prices ever seen. Payers have shown willingness to adopt these therapies despite very high ICURs, often with outcome-based reimbursement agreements. At GBP 1.79 million (\$2.56 million) Zolgensma is one of the most expensive drugs worldwide and was recommended by NICE for very young patients.<sup>79</sup> Strimvelis has a price of €594 000 (\$841 000) per person and is recommended by health authorities in England and Italy. Kymriah and Yescarta were recommended in England at a confidential discounted price under the Cancer Drugs Fund.<sup>80</sup>

Valoctocogene roxaparvovec for hemophilia A falls in the bottom right quadrant (Appendix Fig. S4 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). Rind et al<sup>41</sup> estimated that the expected lifetime cost savings compared with factor VIII might be \$5 million per patient, but regulators in Europe and the United States denied marketing approval<sup>81</sup> because the effectiveness of this gene therapy was then thought to wane over time. Payers are also sometimes disposed to reject ATMPs. EMA gave CMA for Zynteglo for a rare blood disorder, but the sponsor was not able to demonstrate positive net benefit for payers in key European systems.<sup>70,82,83</sup> In contrast, darvadstrocel (Alofisel) was adopted by Spain, France, and Germany<sup>70,84</sup> at a price of \$75 000 to \$88 000 based on minimal information about cost-effectiveness.<sup>54</sup> Stakeholders state that they sometimes find it difficult to anticipate which medicines are likely to be financed.<sup>82</sup> Consistency and clarity about the evidence requirements and criteria for P&R would help stakeholders navigate the HTA process and target investment capital more effectively.<sup>85,86</sup> The forthcoming European Union regulation on HTA is intended as a step toward this goal with the harmonization of clinical evidence assessment.<sup>87</sup> Not all ATMPs offer step changes. There are several examples where benefits are modest and incremental (Appendix Fig. S3 in Supplementary Materials 4 found at <https://doi.org/10.1016/j.jval.2022.07.004>). It would seem reasonable that the default position should be for routine HTA evidentiary requirements, procedures, and criteria to apply in these cases.

### Managing Uncertainty

To manage high uncertainty, regulatory agencies are increasingly granting CMA or exceptional circumstances and mandating postauthorization safety and efficacy studies.<sup>88,89</sup> Between 2006 and 2020, a total of 59 medicines were approved with CMA, 50% of these in the last 4 years.<sup>90</sup> Likewise, payers faced with ATMPs that demand an up-front payment of hundreds of thousands of dollars, coupled with uncertainty about whether a long-term cure will be achieved, are increasingly turning to outcome-based reimbursement agreements. Payers are also concerned about impact on budgets as new ATMPs are approved or therapies approved in one indication show promise in others. For example, there are currently 3 ongoing phase III RCTs that aim to explore the benefits of moving the currently approved CD-19 CAR Ts in R/R DLBCL into the second line setting by challenging autologous stem cell transplant (NCT03391466, NCT03570892, NCT03575351).<sup>91</sup> Hence, health ministries have initiated proprietary data collection

systems to support outcome-based reimbursement and monitor clinical progress.<sup>92</sup> Cross-border initiatives such as the EU Data Analysis and Real World Interrogation Network are still in early stages.<sup>93</sup> Given that these are often rare diseases, data protectionism will limit researchers' ability to resolve key uncertainties. European regulators and national payers should accelerate efforts for alignment and apply minimum common standards.<sup>94,95</sup> Furthermore, intervention registries do not address the problem of uncertainty about outcomes with current SOC.<sup>95</sup> Therefore, it may also be advantageous consider greater use of "disease" registries rather than "intervention" registries.<sup>96,97</sup>

### Use of ATMP Without Centralized Marketing Approval

Commercial ACI therapies have not prospered in Europe despite obtaining both marketing authorization from EMA and adoption recommendations from HTA agencies in England and Spain.<sup>2,98</sup> One of the reasons suggested for withdrawal of the commercial ACIs was that hospitals were able to obtain similar products more cheaply under hospital exemption.<sup>99</sup> European hospital exemption regulation allows national regulators, without centralized approval, to authorize and supervise the nonroutine use of an innovative therapy for patients who lack therapeutic alternatives. Nevertheless, there is wide variation between member states concerning the authorization process, evidence requirements, conditions for use and supervision arrangements, and a general lack of transparency.<sup>99</sup>

### Risk of Bias Arising From Conflict of Interest

This review has noted a particular risk of bias associated with conflict of interest. The studies of CAR T-cell therapy and Luxturna sponsored by manufacturers seemed to predict greater health gains than those produced by research centers without direct financial interest, although the models were based essentially on the same landmark clinical studies. HTA agencies such as NICE and Scottish Medicines Agency have broadly accepted the manufacturers' estimates in these 2 cases. Given that these models are predictions of future effect based on extrapolation from limited current evidence, it is impossible of course to know the "true" effect size. In almost all other respects, these models scored highly in terms of the quality of their analyses and reporting. Nevertheless, industry-funded models sometimes seem to make subtle choices that favor the sponsor, and payers need to be mindful of the risk of bias when evaluating such models, ensure thorough validation, and continue evidence generation.<sup>100</sup>

### Strengths and Weaknesses of This Review

We have systematically reviewed a heterogeneous set of economic studies of ATMP across multiple pathologies and countries. This enabled us to take a broad overview of the state-of-the-art in economic evaluation in these areas and compare sources of evidence, modeling assumptions, and risk of bias where possible. This approach has a number of weaknesses. Comparison of economic analyses across countries must always be undertaken cautiously given that outcomes are conditioned by the local healthcare system, prices, and treatment guidelines. Definition and classification of ATMPs are usually conducted by regulatory authorities during the marketing approval process. In cases where marketing approval was not yet requested, we classified the therapies according to our interpretation of current European Union regulation. Studies were not always clear about the sources of their clinical data. Where possible, we followed up citations where we needed more information about sample sizes, follow-up, and other details. In publications where reporting was

restricted by commercial confidentiality, we made educated guesses about the QALYs associated with ATMP strategies based on the available information. Likewise, price data were often confidential. By comparing reported results, we made some very approximate guesses about what these confidential prices might be in different jurisdictions.

## Conclusions and Recommendations for Analysts and Policy Makers

Our main findings and the conclusions we draw from these are summarized in [Table 5](#).

Evaluation of ATMPs is challenging. Nevertheless, innovation should not proceed without evaluation.<sup>101</sup> Regulators and payers have accepted small studies, particularly in rare diseases, provided other aspects of study design (follow-up, adequacy of endpoints) are adequate, as shown by Strimvelis and Luxturna. Heterogeneity must be considered if data are pooled.

Single-arm studies are often used where current SOC is considered ineffective. Regulators have accepted these to demonstrate efficacy, but this presents a challenge for HTA where assessment of added therapeutic benefit and value for money requires a quantitative analysis against a comparator. This review has identified various approaches using historical controls. Analysts need to be transparent about the assumptions and limitations inherent in their chosen method and properly quantify the degree of uncertainty.<sup>34</sup>

Studies in these therapies are sometimes short term and use surrogate outcomes with weak association with QOL and survival. This is problematic and regulators have rejected applications for marketing approval in such cases. This review has identified various statistical approaches to gain further insight from the available data, such as mixture cure fraction models. As before, analysts need to be transparent about their assumptions and limitations. Clinical trialists (and their sponsors) should be aware of the need to collect health-related QOL, preferably using generic instruments, alongside other measures.

Where clinical data are immature (short term), regulators may place conditions on the marketing approval for additional monitoring, or payers may collect further data as a requirement of managed entry agreements. Hence, there is a patchwork of post-marketing surveillance platforms operated by different actors (regulators, patient organizations, healthcare providers, and manufacturers) and lack of sharing. Sponsors should aim for collaboration, compatibility, and interchange of data registers, especially for rare diseases.

P&R decisions are assessed by the competent authority in each country. So far in the field of ATMP, only Kymriah and Yescarta have achieved reimbursement in the European major 5 countries (Italy, UK, France, Germany, and Spain). Opinions differed about Holoclar, Imylogic, Strimvelis, Spherox, and Alofisel. Although different criteria are understandable, payers should aim for consistency and clarity to facilitate developers' decisions about investment. Meaningful engagement of all stakeholders (including patient groups) is needed to properly value ATMP. There has been debate about whether HTA agencies should apply "special" criteria for ATMP.<sup>12,13</sup> As a general rule, it would seem reasonable that routine HTA evidence requirements and criteria should be applied unless there is a strong case otherwise. Hospital exemption should be reviewed to ensure transparency and best interests of patients. Finally, payers increasingly rely on industry-sponsored economic analyses but critical review needs to be exercised because of conflict of interests.

## Supplemental Material

Supplementary data and a glossary of abbreviations associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2022.07.004>.

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