A Comparative Analysis of Cost-Effectiveness Evaluations of Cell and Gene Therapies across HTA Organisations

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Introduction

Cell and gene therapies (CGTs) are novel, complex treatments that pose specific challenges for payers. High upfront costs and uncertainties over long-term effects can be especially problematic for assessments reliant on cost-effectiveness calculations. Health technology assessment (HTA) processes used across the world were developed before the commercial advent of CGTs, so are not designed to assess these therapies. With the increasing number of high-cost CGTs likely to strain healthcare budgets, it will be increasingly important to adapt existing HTA frameworks.

HTA agencies have made efforts to modify processes to assess the value of high-cost therapies, such as the collaboration between the National Institute of Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institute for Clinical and Economic Review (ICER) to update the ICER value framework, which was implemented by ICER in January 2020[1]. Such multinational HTA collaborations to review methods or conduct joint assessments could become more important and common for CGTs.

This research compared assessments of CGTs across cost-effectiveness HTA organisations to understand how assessment methodologies vary and how this impacts outcomes.

Method

Six HTA organisations were selected due to their use of cost-effectiveness and participation in international HTA collaborations (CADTH, ICER, NICE, Scottish Medicines Consortium [SMC], Dental and Pharmaceutical Benefits Agency [TLV], The National Healthcare Institute [ZIN]). Information was sourced from official agency websites, peer reviewed publications and grey literature to understand each organisation's methods and policies.

HTA reports published by June 2020 from the scope organisations were retrieved for three CGTs case studies (tisagenlecleucel, axicabtagene ciloleucel, voretigene neparvovec) to investigate timelines, HTA processes, cost per quality-adjusted life year (QALY) outcomes and recommendations.

Results:

Comparison of HTA organisation methodologies

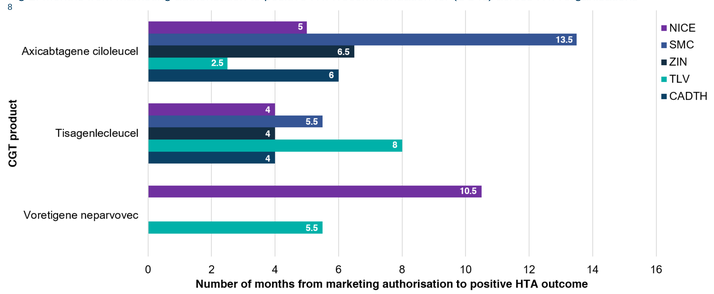
Figure 1: CGT time to market & cost-effectiveness outcomes

Country	England	Scotland	Netherlands	Canada	Sweden	United States
Agency Name[9-19]	NICE National Institute for Health and Care Excellence	Scottish Medicines Consortium	Zorginstituut Nederland	CADTH Evidence Driven.	TLV Tandvårds- och läkemedelsförmånsverket	ICER Institute for Clinical and Economic Review
Agency Type	National HTA agency	National HTA agency	National HTA agency	National HTA agency	National HTA agency	Not For Profit
Types of Recommendations	• Recommended for routine NHS commissioning • Recommendation via Cancer Drugs Fund	• Recommended for routine NHS commissioning	• Reimbursed in the basic package	• Recommended to participating drug plans to determine reimbursement	• Performs analysis for NT Council, which is final reimbursement decision-maker	• Policy recommendations for payers • Discount needed to meet CE thresholds
Impact of Recommendations	Mandatory	Mandatory	Mandatory	Not mandatory	Not mandatory	Not mandatory
CE Thresholds[16]	• STA: £20k-30k per QALY • End of life: £50k per QALY • HST: £100k-300k per QALY	• £20k-30k per QALY commonly assumed • Higher threshold (unspecified) accepted if modifiers are used	• Lowest threshold is €20,000 per QALY • Highest threshold is €80,000 per QALY	• $50,000 per QALY is referred to in reports, however higher ICERs have been accepted	• SEK 700,000-1,220,000 commonly assumed	• $100,000-150,000 per QALY
Implicit / Explicit threshold(s)[16]	Explicit	Implicit	Implicit	Implicit	Implicit	Explicit
Process modifications for high-cost ODs	✓	✓	✓	✓	✓	✓
Process modifications for CGTs	X	X	X	✓	X	✓
Average time for review (according to organisation)	STA: 40-49 weeks HST: 17-27 weeks	18-26 weeks	180 days	180 days	180 days	N/A

- The role of cost-effectiveness analyses in the HTA recommendation and use of cost per QALY thresholds varies significantly. Thresholds range from a potential low of €20,000 per QALY with ZIN to a high of €127,000 ($150,000) with ICER. Factors including high unmet need, significant impact on life expectancy and orphan drug status can lead to higher acceptable costs per QALY.
- NICE and ICER employ explicit cost per QALY thresholds. CADTH, SMC, TLV and ZIN have implicit thresholds that are not clearly defined and can change according to specific circumstances.
- Process modifications for high-cost orphan drugs are utilised by all HTA organisations, to various degrees. However, process adaptations for CGTs were specified by only two HTA organisations (CADTH and ICER). ICER's recent framework for high-cost single and short-term therapies (SSTs) includes consideration of additional elements of value, uncertainties on long-term cost-effectiveness and threshold analyses for durability of effect[9].
- Unlike the other HTA organisations, ICER has no official role in determining reimbursement outcomes. Many payers in the US & overseas do reference their findings when making reimbursement decisions.

CGT time to market & cost-effectiveness outcomes

Fig 2: Months from marketing authorisation to positive HTA recommendation for (CGTs) across HTA organisations[4-8]



Note: *ICER was excluded from this analysis, as ICER has no official role in P&R decisions in its country, and its review timelines are not definitively linked to marketing authorisations*

- The time from marketing authorisation to HTA recommendation was generally shorter for the products analysed compared with standard timelines[2,3]. The average time to positive recommendation for tisagenlecleucel was ~5 months, and for axicabtagene ciloleucel was ~6.5 months. The SMC review of axicabtagene ciloleucel is an outlier at 13.5 months due to the initial negative decision before a resubmission yielded a positive outcome.
- Information on the start date of HTA appraisal was available from NICE, CADTH and ICER. The average time for review by CADTH was ~5.5 months, for NICE was ~11 months. This included a 9-month review of voretigene neparvovec, despite being assessed via the Highly Specialised Technology (HST) route.

Figure 3.1: Cost-effectiveness outcomes across select HTA organisations for **axicabtagene ciloleucel**

Country	HTA Body	Incremental cost-effectiveness ratio* (per QALY, €)	Cost-effectiveness	Cost-effectiveness breakdown
England	NICE[27]	55,000	**Potential to be cost-effective**	Recommended for use within the Cancer Drugs Fund, taking into account the PAS
Scotland	SMC[28]	54,050	**Cost-effective**	Recommended, after application of appropriate SMC modifiers, considering output from the PACE process, taking PAS into account
Netherlands	ZIN[29]	>80,000	**Potential to be cost-effective**	Eligible for inclusion in the basic package, if a lower price agreed
Canada	CADTH[30]	144,724	**Potential to be cost-effective**	On the condition there is a reduction in price; 45-65% price reduction necessary to ensure cost-effectiveness outcome is within the appropriate threshold
Sweden	TLV[31,32]	96,000 - 134,000	**Cost-effective**	Recommended with follow-up data collection requirements
United States	ICER[26]	117,059	**Cost-effective**	Met commonly-cited cost-effectiveness thresholds

ICER estimates were provided in the local currency in the HTA reports. These were converted to EUR using the following conversion rates:
1 USD = 0.85 EUR, 1 GBP = 1.1 EUR, 1 SEK = 0.096 EUR, 1 CAD = 0.64 EUR

Figure 3.2: Cost-effectiveness outcomes across select HTA organisations for **tisagenlecleucel**

Country	HTA Body	Incremental cost-effectiveness ratio* (per QALY, €)	Cost-effectiveness	Cost-effectiveness breakdown
England	NICE[20]	53,092	**Potential to be cost-effective**	Recommended for use within the Cancer Drugs Fund, taking into account the PAS
Scotland	SMC[21]	27,762	**Cost-effective**	Recommended, after application of appropriate SMC modifiers, considering output from the PACE process, and taking into account the PAS
Netherlands	ZIN[22]	Not determined	**Potential to be cost-effective**	Cost-effectiveness not determined, but expected budget impact low so eligible for inclusion in the basic package
Canada	CADTH[23]	34,092	**Potential to be cost-effective**	10% price reduction necessary to ensure cost-effectiveness outcome is within the appropriate threshold
Sweden	TLV[24,25]	48,000 – 105,000	**Cost-effective**	Recommended with follow up data collection requirements
United States	ICER[26]	39,844	**Cost-effective**	Met commonly-cited cost-effectiveness thresholds

ICER estimates were provided in the local currency in the HTA reports. These were converted to EUR using the following conversion rates:
1 USD = 0.85 EUR, 1 GBP = 1.1 EUR, 1 SEK = 0.096 EUR, 1 CAD = 0.64 EUR

Figure 3.3: Cost-effectiveness outcomes across select HTA organisations for **voretigene neparvovec**

Country	HTA Body	Incremental cost-effectiveness ratio* (per QALY, €)	Cost-effectiveness	Cost-effectiveness breakdown
England	NICE[33]	126,452	**Cost-effective**	Recommended for routine NHS use
Scotland	SMC	N/A	**N/A**	N/A
Netherlands	ZIN	N/A	**N/A**	N/A
Canada	CADTH	N/A	**N/A**	N/A
Sweden	TLV[34,35]	173,000 – 289,000	**Not cost-effective**	TBC
United States	ICER[36]	408,111	**Not cost-effective**	Did not meet commonly-cited cost-effectiveness thresholds. However, was found to be cost-effective in the younger population from a modified societal perspective

ICER estimates were provided in the local currency in the HTA reports. These were converted to EUR using the following conversion rates:
1 USD = 0.85 EUR, 1 GBP = 1.1 EUR, 1 SEK = 0.096 EUR, 1 CAD = 0.64 EUR

- Across the products analysed, there was considerable variation in the cost per QALY estimates between HTA organisations. For tisagenlecleucel, there was a 63% difference between the highest and lowest cost per QALY estimates. Despite this significant variation, HTA outcomes for tisagenlecleucel and axicabtagene ciloleucel were almost universally positive, with only CADTH proposing price reductions.
- In the Netherlands, cost-effectiveness assessments are not triggered when expected budget impact is low, which was the case for tisagenlecleucel. A cost per QALY estimate was not determined, but reimbursement was recommended by ZIN.

Case Study: Voretigene neparvovec

The difference between the cost per QALY estimates from ICER and NICE was significant, with ICER's estimate approximately 3.2x greater than that of NICE (€408,111 vs €126,452)

Key reasons for assessment differences:

- **Long-term efficacy**: NICE considered that the long-term duration of effect was biologically plausible, whereas ICER noted this remained uncertain and modelled a shorter treatment effect
- **Endpoint relevance**: ICER considered the novel primary endpoint (multi-luminance mobility test, MLMT) as highly uncertain, as it has not been correlated to real-world outcomes. However, NICE concluded that MLMT was an acceptable endpoint to measure efficacy in the short-term, supported by additional efficacy endpoints

Voretigene neparvovec was assessed via the NICE HST pathway, which is only possible for ultra-orphan drugs. This pathway is associated with a significantly higher cost-effectiveness threshold (£1000,000 - £300,000 per QALY) than the standard process.

Discussion

Despite the different cost per QALY estimates from HTA organisations, differences in the cost-effectiveness thresholds allowed for largely positive recommendations. NICE and SMC both employed process modifications that were vital in the resulting positive reimbursement decisions for tisagenlecleucel and axicabtagene ciloleucel:

- **England:** Tisagenlecleucel was recommended for the Cancer Drugs Fund (CDF), which enables patient access to cancer therapies when the clinical evidence is uncertain but there is potential for the therapy to be cost-effective[37]. Limitations in clinical evidence often lead to uncertain cost-effectiveness estimates, but these can be mitigated with a CDF managed access agreement while further data is collected through the National Health Service (NHS) or clinical studies.
- **Scotland:** The SMC does not use formal cost-effectiveness thresholds, which enables the adaptation of its assessment process with modifiers which are likely to be relevant to innovative CGTs. In addition, for orphan drugs and end-of-life therapies, Patient and Clinician Engagement (PACE) groups can provide an additional perspective in situations where factors beyond cost-effectiveness are relevant. Modifiers and outputs from the PACE process may in part explain the lower cost per QALY estimates due to the reduced uncertainty in evidence and higher willingness-to-pay.

Since reviewing voretigene neparvovec, ICER has updated its methods for assessing high-impact single and short-term therapies (SSTs). The impact of the new framework on the cost-effectiveness outcomes of CGTs remains to be seen, but the incorporation of cost-offsets and other measures of value could make assessments more favourable. Equally, uncertainties around long-term cost-effectiveness may present a barrier for these therapies.

Conclusion

While several organisations employ process modifications for high-cost therapies, few are CGT-specific. Organisations differ in how they handle data uncertainties, higher upfront costs, and long-term data extrapolation, resulting in varied cost per QALY outcomes.

Although the CGT HTA outcomes observed have been largely positive, a major reason for this is the indications in which they have launched. Oncology and rare diseases are often associated with high willingness-to-pay from HTA organisations, so higher cost per QALY outcomes are more likely to be acceptable. In the future, with many CGTs launching and some launching in larger and varied indications, the current pricing and reimbursement (P&R) model may not be sustainable.

Healthcare systems will have to adapt to the changing CGT environment to ensure that patient access to CGTs is not compromised. International collaborations provide opportunities for HTA bodies to share learnings as more CGTs undergo HTA appraisals. These collaborations will only become more important as CGTs become more mainstream and current P&R models are stretched to their limits.

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