How novel is ICER methods guidance on high-impact, single, and short-term therapies?

Patricia Aluko, James Beggs, and Anja K Pownell, PRMA Consulting Ltd, Fleet, UK

Introduction

- Innovative cell and gene therapies (CAGT) are often single-administration treatments with the potential to provide long-term health gains and a possible cure.
- However, they are often associated with high, unrecoverable upfront costs and uncertainty about the extent and duration of clinical outcomes:[1-4]
  - The therapies often target very small patient populations, which makes it difficult to generate robust clinical evidence and to assess the clinical value.
  - Clinical benefits and savings are accrued over a long period (potentially a lifetime), but data are likely to be immature at the time of HTA submission.
  - Payers are concerned about the affordability of these emerging treatments under the existing paradigms of pricing and payments.
- As with other therapies, the value of CAGTs is determined in relation to their incremental costs.
- However, given the unique challenges for CAGTs, organizations assessing the value of healthcare technologies, such as the National Institute for Health and Care Excellence (NICE) in the UK, and the Institute for Clinical and Economic Review (ICER) in the US, are considering alternative novel methods to evaluate both the clinical and cost-effectiveness of these therapies. These alternative methods are necessary to develop an appropriate value-based pricing structure for CAGT treatments that have the potential to achieve cure.[5]

Methods

- We examined the adapted methods for assessing high-impact "Single and Short-term Therapies" (SSTs), developed by ICER and published in November 2019.[6]
- In addition, we reviewed recent health technology assessments (HTAs) of tisagenlecleucel and voretigene neparvovec by NICE and the Scottish Medicines Consortium (SMC), to compare ICER's new framework with the framework for SSTs employed by NICE and evaluations of SSTs by the SMC.

Results

- Areas of uncertainty around the benefit of high-impact SSTs for decision-makers were identified by ICER. These include the duration of benefit, magnitude or quality of benefit, proportion of patients who achieve a specific benefit, different types of survival models, and relative treatment benefit under alternative assumptions.[6]
- The novel methods recently employed by ICER in the US when assessing SSTs, consider the parameters summarized in Table 1 to address these areas of uncertainty.[5]

Table 1. Key parameters used by ICER (US) when assessing SSTs

Parameters	Definition/approach used
Determining treatments for which adapted assessment methods will be used	
Definition of therapies in scope	High-impact SSTs, which must be a combination of short-term treatment with the potential for substantial long-term gain (subcategories: potential cures and high-impact therapies).
Assessing and describing uncertainty	
Cure proportion modeling	Survival analysis will be carried out to address uncertainty. Cure proportion modeling is applicable where a proportion of patients may be expected to benefit from the treatment stopping the progression of a severe disease, or to be cured of the disease.
Optimistic and conservative benefit scenarios for healthcare system perspective base case	In addition to the base case and associated sensitivity analyses, ICER applies two scenario analyses to reflect an optimistic and a conservative assumption regarding the benefit of SSTs under review.
Threshold analysis for durability of effect	When the SST price is known or can be estimated, assessments will also include a scenario with a threshold analysis determining the duration of beneficial effect (e.g., cure) for those patients receiving short-term benefit that would be needed to achieve standard cost-effectiveness thresholds (e.g., $150,000/QALY) gained.
Addressing uncertainties around the economic models	Discussion around the model structure and inputs suggested by manufacturers and/or stakeholders.
Time divergence between costs and benefits	
Discounting	3% discounting is applied to both health and outcome costs.
Sharing of Health System Savings	
Shared savings scenarios	50/50 shared savings model and cost-offset cap model.
Additional elements of value	
Additional elements of value	Qualitative review of patient views of the risks and benefits of alternatives, including consideration of the value of treatment choice and the potential benefits or disadvantages of option value.

- The adapted ICER methods require cure-fraction modeling, discounting of outcomes and costs at the standard 3%, and a threshold analysis of the duration of the beneficial effect. A cost-effectiveness threshold of $150,000 per quality-adjusted life-year (QALY) gained is used to guide evaluation of long-term value for money. ICER will also consider benefits beyond QALYs, including the value of treatment choice and potential benefit or disadvantage of option value.
- Parameters proposed by the adapted ICER methods in the US (Table 1) were extracted from representative HTAs (tisagenlecleucel and voretigene neparvovec) carried out by NICE and SMC in the UK.
- In agreement with ICER's methods in the US, NICE and SMC in the UK accepted cure-fraction models for tisagenlecleucel but not voretigene neparvovec. NICE accepted a discount rate of 3.5% for tisagenlecleucel in acute lymphoblastic leukemia (ALL) and a rate of 3.5% and 1.5% for voretigene neparvovec. NICE acknowledged value beyond health benefits for voretigene neparvovec, while the SMC did so for tisagenlecleucel (the manufacturer attempted to include these benefits in their submission; the assessment is ongoing). Some of the value beyond health benefits acknowledged by NICE include patients retaining independence and research enabling the advancement of the broader field of CAGT. The SMC accepted the additional value in single administration, and reduced patient and carer burden resulting from these treatments.
- Both NICE and the SMC applied higher cost-effectiveness thresholds for ultra-rare diseases.
- In the HTA of voretigene neparvovec, different scenarios were considered for the treatment effect duration. NICE accepted the assumption that the treatment effect would span at least 20 years despite the lack of long-term data.
- Both NICE and SMC assessments took into account the duration of treatment and discussed the limitations of economic modeling.
- Neither NICE nor the SMC directly discussed optimistic and conservative benefit scenarios or hypothetical shared savings scenarios, in contrast with ICER's published guidance.

Table 2: Details of product extractions

ICER methods	NICE			SMC		
	Tisagenlecleucel in DLBCL[7,8]	Tisagenlecleucel in ALL[9]	Voretigene neparvovec[10]	Tisagenlecleucel in DLBCL[11]	Tisagenlecleucel in ALL[12]	Voretigene neparvovec[13] Ultra-orphan initial assessment; ongoing
Cure proportion modeling used	Yes	Yes	Not included	Cure assumption used	Yes	Not included
Optimistic/ conservative benefit scenarios included	Not included	Not included	Explored and accepted the scenarios for 20 and 40 years' treatment benefit	Not included	Not included	Not included
Threshold of treatment durability analysis	Unknown	Unknown	Yes: assessment of duration of treatment effect	Yes: assessment of time horizon scenarios	Yes: assessment of time horizon scenarios	Yes: assessment of duration of treatment effect
Discount rate: 3% discounting applied to health and outcome costs	3.5%	3.5% (1.5% deemed unacceptable as treatment does not offer sustained health benefit of at least 30 years)	3.5% preferred by committee, 1.5% considered acceptable due to long term benefit which spans beyond 30 years	Unknown	Unknown	Unknown
Shared savings scenarios: 50/50 shared savings model and cost-offset cap model	Not included	Not included	Not included	Not included	Not included	Not included
Additional elements of value Qualitative review of patient views of the risks and benefits of alternatives, including consideration of the value of treatment choice and the potential benefits or disadvantages of option value.	There are no additional benefits that had not been captured in the economic analysis.	There are no additional benefits that had not been captured in the economic analysis.	Voretigene neparvovec has an effect beyond health benefits but the impact on the cost-effectiveness would be small Voretigene neparvovec met the criteria for a QALY weighting to be applied. The uncertainties were acknowledged and benefits that were not captured in the analysis were considered.	The benefits of tisagenlecleucel were considered in the context of the decision modifiers that can be applied in cases of high cost-effectiveness ratios. Greater uncertainty in the economic case was accepted given the ultra-orphan status.	The benefits of tisagenlecleucel were considered in the context of the decision modifiers that can be applied in cases of high cost-effectiveness ratios. Greater uncertainty in the economic case was accepted given the ultra-orphan status.	The manufacturer tried to capture some of the effects of treatment on carers and the wider economic impact in the economic analysis.

Blue shading indicates parameters where ICER methods differ from those of NICE/SMC.

Conclusions

- Both NICE and SMC applied higher cost-effectiveness thresholds than the ICER threshold of £30,000 when considering ultra-rare diseases.
- While higher cost-effectiveness thresholds and cure-fraction models are already considered in HTAs of costly SSTs in the UK, ICER's approach to determining the value of treatment choice and option value is novel.
- NICE and the SMC already consider many of the parameters from ICER's SST framework; incorporating the other parameters in future evaluations may be beneficial.
- ICER plans to implement the adapted methods in January 2020 but has yet to publish or update their previous assessments according to the updated framework. Therefore, a review of future ICER assessments will indicate whether the new methodology provides a better way to demonstrate the value of potentially curative treatments.
- NICE guidance from 2017 for HSTs with plausible incremental cost-effectiveness ratios of >£100,000 per QALY gained, recommends considering the following factors when evaluating the acceptability of a technology: certainty around the incremental cost-effectiveness ratio, evidence of uncaptured health utility gains, innovation with benefits not captured by QALY value, magnitude of incremental therapeutic improvement, and aspects relating to non-health objectives of the National Health Service. Further guidance on methodology would benefit applications for CAGT products.
- A review of future ICER assessments will indicate whether the new methodology provides a better way to demonstrate the value of potentially curative treatments.

Limitations

- It is too early to know whether any of the novel concepts incorporated by ICER's framework for review of SSTs in the US will address the challenges of demonstrating long-term value well enough to overcome short-term affordability concerns for CAGT products.
- This analysis was limited to three agencies and assessments of two products. Further studies are required to validate these findings and extrapolate these observations to other products and markets.

References

1. Abou-El-Enein M, Bauer G, Medcalf N, *et al*. Putting a price tag on novel autologous cellular therapies. Cytotherapy 2016;18: 1056-1061.
2. Salzman R, Cook F, Hunt T, *et al*. Addressing the value of gene therapy and enhancing patient access to transformative treatments. Mol Ther. 2018;26 (1):2717-2726.
3. Hampson G, Towse A, Pearson SD, *et al*. Gene therapy: Evidence, value, and affordability in the US healthcare system. J Comp Eff Res. 2018;7 (1):15-28.
4. ICER. Gener Therapy White Paper. 2017.
5. ICER. Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief. 2019.
6. ICER. Adapted Value assessment Methods for High-Impact "Single and Short-term Therapies" (SSTs). 2019.
7. NICE. Tisagenleleucel (TA567): Technology Appraisal Guidance. 2019.
8. NICE. Tisagenlecleucel (TA567): Committee Papers. 2019.
9. NICE. Tisagenlecleucel (TA554): Technology Appraisal Guidance. 2018.
10. NICE. Voretigene neparvovec (HST11): Highly Specialised Technologies Appraisal Guidance. 2019.
11. SMC. Tisagenlecleucel (SMC2200). 2019.
12. SMC. Tisagenlecleucel (SMC2129). 2019.
13. SMC. Voretigene neparvovec (SMC2228). 2019.
14. NICE. HST Guidance. 2017.

Acknowledgments

This work was conducted and funded by PRMA Consulting with contributions from Jennifer Sander and Dr Marie Chivers.