Use of external control arms in reimbursement submissions: a review of CAR-T appraisals by NICE and CDA

Comentale S[1], Wallace M[2], Messina P[1], Daniel S[3], Jin G[2], Szende A[2]

[1]Fortrea Market Access Consulting & HEOR, Milan, Italy;
[2]Fortrea Market Access Consulting & HEOR, Maidenhead, United Kingdom;
[3]Fortrea Market Access Consulting & HEOR, Tel Aviv, Israel

Introduction

- A single-arm trial with an external control arm (ECA) is one in which the patients in the control group do not participate in the trial. In these instances, an external control arm (ECA) can provide context for single-arm trial evidence.[1]
- ECA trials are increasingly common due to practical and ethical considerations, particularly in rare diseases with high unmet need.[1]
- Chimeric antigen receptor (CAR)-T cell therapies, targeting rare conditions, often cannot be ethically or practically evaluated through randomised controlled trials (RCTs).[2]
- This study examines methodological considerations for ECAs and their acceptance by health technology assessment (HTA) bodies, focusing on CAR-T cell therapies appraised by the National Institute for Health and Care Excellence (NICE) in the United Kingdom and Canada's Drug Agency (CDA).

Methods

- A review of NICE and CDA websites identified published CAR-T cell therapy appraisals using ECA evidence (up to June 2024).
- Key details regarding ECA sources, statistical methods, economic models, agency critiques of evidence submissions were extracted for review; reimbursement decisions were also collected.

Results

- Of 14 identified appraisals, 12 described the use of an ECA (NICE: 5; CDA: 7). All appraisals were of products for the treatment of relapsed and/or refractory haematological conditions.

ECA sources

- Most evidence submissions used individual patient data from historical clinical trials, retrospective real-world studies, or prospective observational studies to build ECAs. Of all appraisals, 7 (58%) obtained external comparator data from at least one retrospective cohort study and 6 (50%) from at least one clinical trial; 7 (58%) of appraisals used more than one source for external comparator data. 8 (66%) appraisals used individual patient data (IPD) to inform ECAs.
- In one instance (TA894), NICE critiqued the absence of more appropriate sources that used IPD and were available to the manufacturer[3]. On another occasion (PG0304), CDA critiqued a retrospective matched-cohort study as not relevant to Canadian patients[4].

Statistical methods

- The main methods were matching-adjusted indirect comparison (57%), propensity score weighting (29%), and propensity score matching (29%); some evidence submissions used multiple methods (58% of evidence submissions).
- Common agency critiques of statistical approaches included exclusion of prognostic factors, small sample sizes, low data quality, clinical heterogeneity, lack of face validity, and uncertainty in comparative efficacy assessments; CDA criticised statistical methods more frequently than NICE.

Table 1. Statistical approaches and critiques issued by HTA bodies in CAR-T appraisals

Statistical approach	NICE (N=5)	CDA (N=7)
Matching-adjusted indirect comparison (MAIC)	N = 3 • Potential violation of proportional hazards assumption	N = 5 • Lack of prognostic factors or effect modifiers • Small sample size/ESS • Low quality comparator trials • Trials design differences • Differences in trial design
Propensity score matching (PSM)	N = 2 • No major critique	N = 2 • Residual (unmeasured) confounding • Small sample size / wider CIs
Propensity score weighting (PSW)	N = 1 • SMR weighting application to the propensity scoring is unclear. • Small sample size limits effective propensity score model calculation and inclusion of relevant prognostic factors.	N = 3 • Residual confounding due to missing data on observed prognostic factors • Small ESS
Naïve unadjusted comparison	N = 1 • Lack of robust, formal adjustment methods using matching • Wide CIs • Heterogeneity • Potential residual confounding	-
Use of IPD for both 'experimental' and 'comparator' arms	N = 3	N = 5

CI = confidence interval; ESS = effective sample size; IPD = individual patient data; NICE = National Institute for Health and Care Excellence; SMR = standardized mortality ratio.

Economic modelling

- All submissions used partitioned survival models, with one CDA appraisal (PG0302) also employing a decision tree model.
- NICE appraisals reported incremental cost-effectiveness ratios (ICERs) between £20,000 and £58,223 per QALY; CDA appraisals ranged from C$127,679 to C$1,276,217.
- ICERs reflected an elevated degree of uncertainty in cost-effectiveness estimations.
- In five appraisals, CDA critiqued the lack of robust evidence regarding survival extrapolations, while two appraisals were critiqued for comparator choices not aligned with Canadian clinical practice.

HTA outcomes

- Despite numerous issues identified in evidence submissions, 83% of appraisals resulted in a positive recommendation (NICE: 4, CDA: 6).
- Two of NICE's positive recommendations were for interim funding via the Cancer Drugs Fund pending further evidence, due to uncertainties in survival estimates.[5,6]
- One negative decision by CDA was due to a lack of evidence regarding clinical benefit evidence[7], while NICE's only negative recommendation stemmed from highly uncertain economic and clinical benefits resulting in ICERs per QALY considerably above acceptable cost-effectiveness thresholds.[3]

Table 2. Outcomes of CAR-T HTA using ECA by country

Product	Indication	NICE	CDA
Axicabtagene ciloleucel	Diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma	✓	–
Axicabtagene ciloleucel	Follicular lymphoma	–	✓
Brexucabtagene autoleucel	Mantle cell lymphoma	✓*	✓
Brexucabtagene autoleucel	B-cell acute lymphoblastic leukaemia	✓*	–
Brexucabtagene autoleucel	B-cell precursor acute lymphoblastic leukaemia	–	✓
Ciltacabtagene autoleucel	Multiple myeloma	–	✓
Idecabtagene vicleucel	Multiple myeloma	–	–
Lisocabtagene maraleucel	Large B-cell lymphoma	–	✓
Tisagenlecleucel	B-cell acute lymphoblastic leukaemia	✓	–
Tisagenlecleucel	Follicular lymphoma	–	✓

✓ Positive reimbursement recommendation – Negative reimbursement recommendation – Not reported or pending assessment
Recommended for use within the Cancer Drugs Fund

- Table 3 illustrates the case of axicabtagene ciloleucel indicated for follicular lymphoma when both agencies highlighted limitations due to uncertainties in data but reached opposite recommendation decisions.

Table 3. Case study: axicabtagene ciloleucel in relapsed/refractory grade 1, 2, or 3a follicular lymphoma

	NICE (TA894)	CDA (PG0314)
Statistical sources	Retrospective cohort study	Retrospective cohort study
Statistical methods	PSW; unanchored ITC; G-estimation	PSW
Economic model	Partitioned survival model	Partitioned survival model
Estimated ICER	>£40,000	C$243,879 to C$544,875*
Critiques issued	• Unclear SMR weighting • Small sample sizes for PSW • High degree of uncertainty in model due to: • Immature OS data • Lack of validity of assumptions on long-term survival	• Considerable differences between populations after PSW • Residual imbalances in prognostic factors and effect modifiers • Limited evidence to confirm cure model assumption • Underestimation of long-term OS data for SoC • Costs related to CAR-T not adequately considered • Not reflective of Canadian clinical practice
Outcome	Not recommended	Recommended

CDA = Canada's Drug Agency; CAR-T = chimeric antigen receptor T-cell; NICE = National Institute for Health and Care Excellence; OS = overall survival; PSW = propensity score weighting; SMR = standardized mortality ratio; SoC = standard of care
*CDA analysis

Conclusions

- HTA submissions for CAR-T cell therapies based on single-arm trials with ECAs are largely accepted by NICE and CDA.
- Despite methodological issues in evidence submissions, HTA agencies are generally willing to recommend CAR-T cell therapies for reimbursement due to the high unmet need in their target indications.
- Future research endeavours should prioritise exploring the incorporation of prognostic factors and effect modifiers in ECA construction to enhance the robustness and reliability of HTA evaluations.

Abbreviations

CAR-T = Chimeric antigen T-cell, CDA = Canada's Drug Agency, CE = Cost-effectiveness, ECA = External control arm, HTA = Health technology assessment, ICER = incremental cost-effectiveness ratio, NICE = National Institute for Health and Care Excellence, QALY = Quality-adjusted life year.

References

1. Hashmi M, et al. Single-arm oncology trials and the nature of external controls arms. J Comp Effect Res. 2021;10(12):1052–1066.
2. Mikhael J, et al. Chimeric Antigen Receptor T-Cell Therapies: Barriers and Solutions to Access. JCO Oncol Pract. 2022;18(12):800–807.
3. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma [TA894]. Published 7 Jun 2023.
4. Canada's Drug Agency. Brexucabtagene autoleucel [PG0304]. Published 17 Apr 2023.
5. National Institute for Health and Care Excellence. Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [TA677]. Published 24 Feb 2021.
6. National Institute for Health and Care Excellence. Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [TA893]. Published 7 Jun 2023.
7. Canada's Drug Agency. Idecabtagene vicleucel [PG0240]. Published 17 Nov 2021.

ISPOR Europe 2024