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Use of External Control Arms in Pharmaceutical Submissions to the National Institute for Health and Care Excellence for Technology Appraisals: A Targeted Review

MSR121

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BACKGROUND

- Randomised controlled trials (RCTs) are the gold standard to generate comparative evidence for the efficacy and safety of medical interventions.[1]
- However, when RCTs are impractical or unethical to conduct, single-arm trials (SATs) may be used to investigate an experimental treatment. Patient-level data from a source external to the SAT (e.g., from another trial or from real-world evidence [RWE]) may then be used to form an external control arm (ECA) to help establish the comparative efficacy and safety of the experimental treatment.[2]
- ECAs can also be used to supplement the evidence from RCTs. For example, hybrid control arms (i.e., a mix of randomised and external controls) enable the assessment of evidence that may be unavailable in traditional RCTs (e.g., long-term outcomes).[3]

OBJECTIVES

- To identify the frequency of ECA use in determining the comparative efficacy and/or safety of experimental treatments in pharmaceutical submissions to the National Institute for Health and Care Excellence (NICE) for technology appraisals (TAs). Further, to summarise the methods used to derive and analyse ECAs and NICE considerations toward the use of ECAs in recent TAs by therapeutic area and TA outcome.

METHODS

- The NICE website was searched for TA guidance published from 1 January 2022 through 23 May 2023; the terms "external control," "observational," and "real world" were used to narrow the searches. A researcher reviewed the documents underlying each unique TA identified to check whether ECAs were used for the TA and to extract relevant data if ECAs were used.

RESULTS

- The review identified 11/132 (8.3%) NICE TAs published in the timeframe of interest that used ECAs to determine the comparative efficacy of investigated products. The 11 TAs assessed oncology products investigated in SATs; 1 product was also investigated in an RCT. ECAs were used in primary analyses in 8/11 (72.7%) TAs and in supplementary analyses only in 3/11 (27.3%) TAs.
- There were no clear distinctions in the methods used to derive and analyse ECAs and the feedback received on ECAs across TAs by outcome (Table 1). Propensity score weighting analysis (PSWA) was used most frequently—in 7/11 (63.6%) TAs—to increase comparability between patients in the ECAs and experimental trials. The most common feedback, received in 5/11 (45.5%) TAs, noted that the comparison of data from trials and RWE made the analysis results uncertain.
- 4/11 (36.4%) TAs resulted in positive recommendations for product use; NICE found that their analyses had uncertainties but that the cost-effectiveness (CE) estimates were acceptable. 3/11 (27.3%) TAs resulted in managed access agreements for product use within the Cancer Drugs Fund; NICE noted that they presented promising clinical evidence but asked to see further long-term data for the products due to uncertainties in the analyses and CE estimates. 4/11 (36.4%) TAs did not result in recommendations for product use; NICE noted that their analyses had uncertainties and their CE estimates were too high to be considered acceptable.

DISCUSSION

- Our review suggests that certain practices can reduce uncertainty in analyses that use ECAs to generate comparative treatment effects for NICE TAs. Searches for sources of ECAs should be systematic, the comparators included in ECAs should reflect the United Kingdom treatment landscape (where possible), robust statistical methods that account for confounders should be used to increase comparability between ECAs and trial arms, and limitations of analyses should be stated. These practices align with recommendations for ECAs provided in the NICE RWE framework, which should be followed when RWE is used to form an ECA.[4]
- We reviewed technologies appraised through NICE's standard TA programme. Future research could examine the use of ECAs in TAs performed for products that NICE defines as highly specialised technologies.

CONCLUSIONS

NICE has accepted the use of ECAs to generate comparative evidence in some submissions and recognises that such analyses may have uncertainties. NICE considers these analyses alongside the suite of evidence submitted for TAs to determine their recommendations.

REFERENCES

1. Bothwell LE, et al. N Engl J Med. 2016 Jun 2;374(22):2175-81.
2. Mishra-Kalyani PS, et al. Ann Oncol. 2022 Apr 1;33(4):376-83.
3. Burcu M, et al. Pharmacoepidemiol Drug Saf. 2020 Oct;29(10):1228-35.
4. NICE. 2022. https://www.nice.org.uk/corporate/ecd9/chapter/overview.

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Table 1. Methods and Feedback Underlying ECAs in NICE TAs by Outcome

TA No., Product, Indication, Trial	ECA Source, Comparator Treatment(s)	Methods Used to Derive and Analyse ECA	Key Feedback
Positive recommendations			
TA789 • Tepotinib • Non-small cell lung cancer (with METex14-skipping alterations) • SAT: VISION	• RWE (3 non-interventional studies and a Canadian retrospective chart review) • Blended comparator arms (chemotherapies and IOs considered separately)	**Supplementary analysis:** • Inclusion criteria of SAT applied to ECA • PSWA using SMR weights; covariates identified through interviews with clinical experts • HRs for PFS and OS computed	• RCT could have been conducted • Patients in SAT and ECA were not generalisable to patients in the UK • Blended ECAs included treatments not offered in the UK • ITC based on small sample sizes
TA816 • Alpelisib with fulvestrant • Advanced breast cancer (hormone receptor positive, HER2 negative, PIK3CA mutated) • RCT: SOLAR-1; SAT: BYLieve	• RCT (BOLERO-2) • Everolimus + exemestane	**Supplementary analysis:** • PSWA using IPTW (ECA vs. SOLAR-1) • HRs for PFS and OS computed	• Insufficient details on covariate selection for models • In the analysis using RCT data, the benefit of including placebo arms in PS estimation was unclear given ITC was unanchored • Blended ECA in the analysis using RWE includes treatments not offered in the UK • ITCs based on small sample sizes
	• RWE (Flatiron Health's CGDB) • Blended comparator arm (standard of care in the US)	**Supplementary analyses:** • Inclusion criteria of SAT applied to ECA • 3 methods used: – Weighting by odds – PS matching – Exact matching • HRs for PFS and OS computed	
TA855 • Mobocertinib • Non-small cell lung cancer (EGFR exon 20 insertion mutation positive) • SAT: Study AP32788-15-101	• RWE (Flatiron Health study and German retrospective chart review) • Blended comparator arm (chemotherapies, IOs, combination of chemotherapies and IOs, and EGFR TKIs)	**Primary analysis:** • PSWA using IPTW; covariates identified through a TLR and survey of oncologists and verified by experts • HRs for PFS and OS computed	• Unsystematic search for RWE sources • Comparison of data from a trial and RWE makes results uncertain • ECA could have excluded EGFR TKIs (not used in the UK) • Analysis not robust due to unadjusted differences between patients in the SAT and ECA
TA872 • Axicabtagene ciloleucel • Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma • SAT: ZUMA-1	• RWE (retrospective study of 4 pooled databases) • Blended comparator arm (salvage chemotherapy, rituximab maintenance therapy, and observation after autologous stem transplant)	**Primary analysis:** • Inclusion criteria of SAT applied to ECA; unclear whether matching or weighting used • OR for response and HR for OS computed	• Unsystematic search for RWE sources • Studies outside the UK were excluded in the TLR used to identify RWE sources although ZUMA-1 and SCHOLAR-1 were not UK-based • ITC based on small sample size of ECA due to restriction
Resulted in managed-access agreements			
TA 760 • Selpercatinib • Non-small cell lung cancer (RET fusion positive) • SAT: LIBRETTO-001	• RCT (REVEL) • Docetaxel	**Primary analysis:** • PS matching (covariates identified through Flatiron Health's CGDB) • NMAs performed to compute OR for response, OS HR, and PFS HR **Supplementary analysis:** • TMLE (covariates as above) • NMAs as above	• Fewer patients included in primary vs. supplementary analysis • Uncertainty in results of supplementary analysis due to multiple complex statistical steps • Proportional hazards assumption violated in other trials in NMA
TA 779 • Dostarlimab • Endometrial cancer with high MSI or MMR deficiency • SAT: GARNET	• RWE (UK National Cancer Registration and Analysis Service) • Blended comparator arm (chemotherapies)	**Primary analysis:** • Inclusion criteria of SAT applied to ECA • Naive comparison of OS and PFS	• Comparison of data from a trial and RWE makes results uncertain • Analysis not robust due to unadjusted differences between patients in the SAT and ECA
TA 781 • Sotorasib • Non-small cell lung cancer (KRAS G12C mutation positive) • SAT: CodeBreaK100	• RWE (Amgen Flatiron Health real-world study) • Blended comparator arm (chemotherapies)	**Supplementary analysis:** • PSWA; covariates identified through literature reviews and physician interviews • HRs for PFS and OS computed	• PSWA adjusted for more covariates than primary MAIC but had a similar ESS • ECA could have been limited to docetaxel • Other methods to adjust ECA could have been explored
Did not result in recommendations for product use			
TA 795 • Ibrutinib • Waldenstrom's macroglobulinaemia • SAT: Study 1118E	• RWE (European retrospective chart review) • Blended comparator arm (2L+ rituximab + chemotherapy options)	**Primary analysis:** • Subset of patients from RWE cohort who matched patients from the SAT based on prior lines of therapy were selected • HR for PFS computed	• Comparison of data from a trial and RWE makes ITC results uncertain • Analysis not robust due to unadjusted differences between patients in the SAT and ECA
TA 812 • Pralsetinib • Non-small cell lung cancer (RET fusion positive) • ARROW	• RCTs (OAK and IMpower 132) • Docetaxel and platinum-based chemotherapy ± pemetrexed considered separately	**Primary analysis:** • PSWA using IPTW • HRs for OS, PFS, and time to treatment discontinuation computed	• Poor quality SAT • Search methods not described for SLR used to identify evidence base for comparators • Comparison of data from a trial and RWE makes supplementary ITC results uncertain • Other statistical methods could have been explored to adjust ECAs
	• RWE (Flatiron Health's CGDB) • Pembrolizumab + pemetrexed + carboplatin, and pembrolizumab considered separately	**Supplementary analysis:** • PSWA using IPTW • Outcomes as above	
TA 850 • Amivantamab • Non-small cell lung cancer (EGFR exon 20 insertion mutation positive) • SAT: CHRYSALIS	• RWE; US cohort (Flatiron Health Spotlight, ConcertAI, and COTA) • Blended comparator arm (chemotherapies and IOs)	**Primary analysis:** • PSWA using IPTW; covariates identified through an SLR and verified by experts • OR for response and HRs for PFS, OS, and TTNT computed	• Unsystematic search for RWE sources • Comparison of data from a trial and RWE makes ITC results uncertain • Use of a blended ECA makes ITC results uncertain • Analysis not robust due to unadjusted differences between patients in the SAT and ECA
	• RWE; UK cohort (National Cancer Registration and Analysis Service) • Blended comparator arm (chemotherapies and IOs)	**Supplementary analysis:** • Multivariable regression (covariates as above) • HRs for OS and TTNT computed	
TA 883 • Tafasitamab with lenalidomide • Diffuse large B-cell lymphoma • SAT: L-MIND	• RWE (retrospective cohort study, RE-MIND2) • 3 comparators considered separately: – Rituximab with gemcitabine and oxaliplatin – Polatuzumab vedotin with bendamustine and rituximab – Bendamustine and rituximab	**Primary analysis for first comparator or else supplementary:** • Nearest-neighbour PS matching • HRs for PFS and OS computed **Supplementary analyses for all comparators:** • PSWA using IPTW • Multivariable regression • Same outcomes as above	• Concerning lack of clarity on methods used for ITC

CGDB = clinic-genomic database; EGFR = epidermal growth factor receptor; ESS = effective sample size; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IO = immunotherapy; IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; MMR = mismatch repair; MSI = microsatellite instability; NMA = network meta-analysis; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PS = propensity score; PSWA = propensity score weighting analysis;SLR = systematic literature review; SMR = standardised mortality ratio; TKI = tyrosine kinase inhibitor; TLR = targeted literature review; TMLE = targeted maximum likelihood estimation; TTNT = time to next treatment; US = United States.

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