Acceptance of Real-World Evidence as Comparative Efficacy in Lieu of Trial Evidence: A Review of Past NICE Appraisals in Oncology

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HTA327

Objective

To assess the acceptance of real-world evidence as a source of comparative efficacy evidence in recent NICE technology appraisals in oncology.

Background

- There has been a significant increase in the use of real-world evidence (RWE) to support reimbursement submissions to the National Institute for Health and Care Excellence (NICE) and other Health Technology Assessment (HTA) agencies worldwide; a trend which appears to be accelerating in recent years.[1]
- The use of RWE may add particular value as a source of evidence to inform comparative efficacy assessment in oncology indications, given that almost a fifth of oncology submissions to NICE between 2017 and 2022 included only single-arm trials.[2]
- However, despite the publication of a framework on the appropriate use of RWE in appraisals, the extent to which NICE is willing to accept RWE as a source of evidence when assessing comparative efficacy remains unclear.[3]

Methods

- The NICE website was searched on the 14 June 2023 to identify the 10 most recent oncology appraisals with published final guidance in which RWE was used as a source of efficacy evidence for one or more of the relevant comparators in the appraisal.
- Key information was systematically extracted for analysis relating to the use of RWE, external assessment group (EAG) and Committee critique of the RWE, and the outcomes of the appraisal.
- Additional information on data provenance and reporting were also extracted.

Results

- Of the 10 appraisals reviewed, 7 received positive recommendations, 2 of which were recommended under the Cancer Drugs Fund (CDF).
- Overall, the EAG and Committee acknowledged the need for RWE, and the use of RWE as efficacy evidence for comparator(s) was accepted as appropriate to a moderate or high degree in 6 of the 10 appraisals (**Figure 1**).
- However, the presented RWE formed part of the EAG's key issues in 8 of the reviewed appraisals and was highlighted by the Committee as a source of uncertainty in 9.
  - Commonly reported concerns by the EAG and Committee included opaque reporting of the provenance, identification and quality of RWE sources.
  - Generalisability of the RWE was also reported as a key source of uncertainty in 5/10 appraisals (**Table 1**). Notably, only 3 of the 10 appraisals used RWE from the UK.
- Statistical methods of adjustment were used to account for heterogeneity in 5 appraisals, however a lack of suitable reporting of statistical methods was noted in 4 of these appraisals.
- The use of RWE was highlighted as a key source of Committee uncertainty in all 3 of the appraisals that received negative recommendations: RWE was noted as a source of uncertainty in 2 of the final appraisal documents (FADs), and was rejected in favour of trial evidence in 1.

Conclusions

This research suggests that EAG and Committee concerns relating to the use of external control arms based on RWE are common in oncology appraisals, even for appraisals which ultimately receive positive recommendations.

Notably, improved reporting of data provenance and handling has been cited by NICE as helping to address Committee concerns in a recently published case study of one of the appraisals explored as part of this research (TA855).[4]

Greater emphasis should be placed on clear and transparent reporting of data provenance, identification of appropriate evidence, and statistical methods of adjustment, in order to alleviate uncertainty inherent in the use of RWE as comparative efficacy data.

FIGURE 1

Appraisal outcomes in recent NICE oncology appraisals

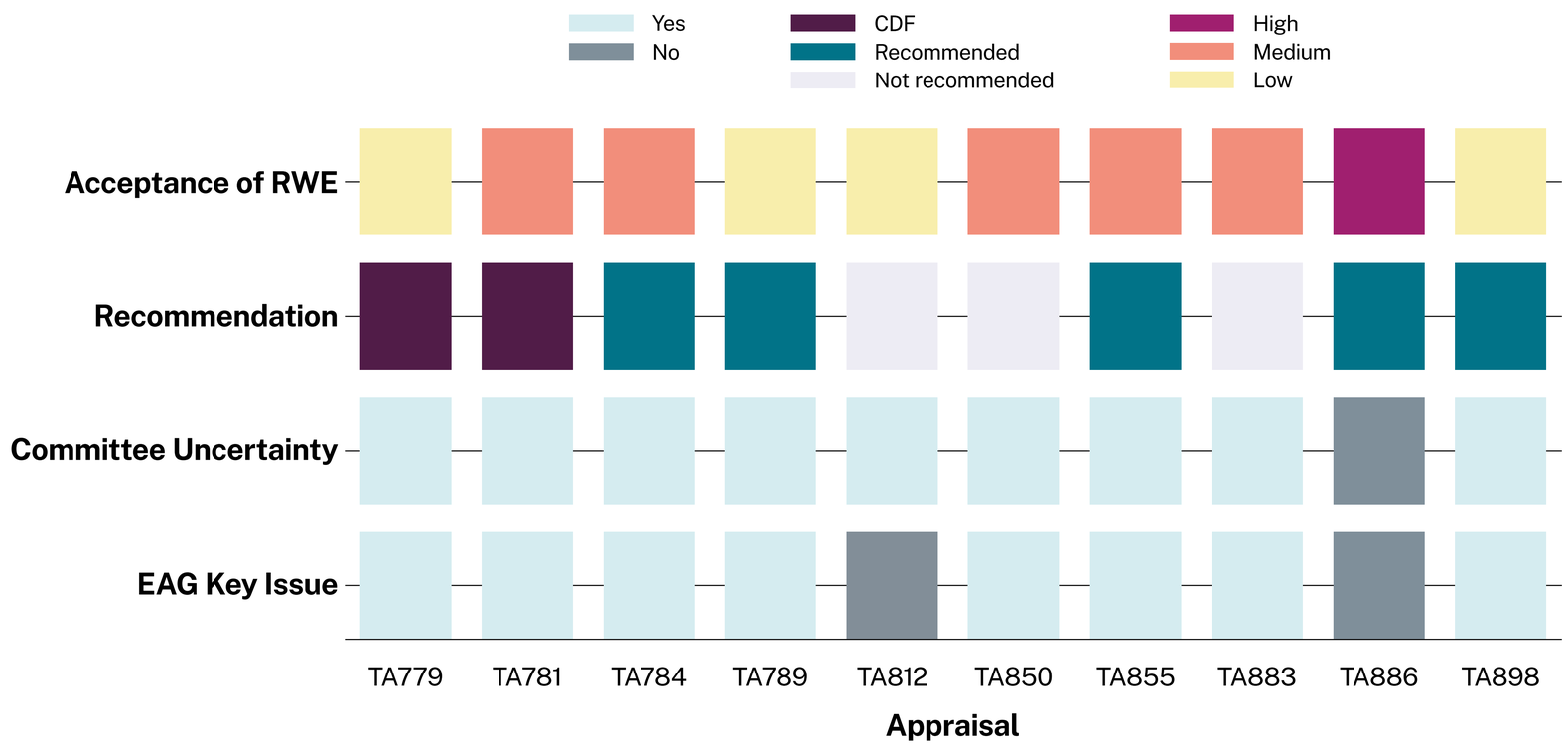

TABLE 1

Summary of RWE use and key uncertainty

Appraisal	Data provenance	Use of RWE	Uncertainty
TA779	NCRAS	Direct comparator efficacy (PFS and OS)	♦ Generalisability: fundamental differences between trial and comparator cohorts ♦ Differences in effect when using RWE data compared to using values within the literature
TA781	Flatiron	Alternative (PSWA) cost-effectiveness analysis (PFS and OS)	♦ Lack of information about treatments included in the RWE, and restricted covariate selection in the PSWA analysis
TA784	SACT Lord *et al.* (2020)	Alternative cost-effectiveness analysis (OS)	♦ Generalisability: differences in baseline characteristics between trial and comparator cohorts ♦ The EAG did not consider the RWE analyses robust because of limitations in a naive comparison between non-randomised real-world sources; lack of baseline characteristics in RWE meant adjustments for differences were not feasible
TA789	Canadian Chart Review	Direct comparator efficacy (PFS and OS)	♦ Lack of data about individual treatments (had to use a grouped comparator) and non-UK RWE meant treatments did not match UK clinical practice
TA812	Flatiron	Indirect treatment comparison (PFS and OS)	♦ RWE limited to a subgroup of patients, affecting generalisability
TA850	Flatiron, COTA, ConcertAI PHE, NHS Digital	Direct comparator efficacy (US) Scenario analysis (UK)	♦ Generalisability: basket of comparators may not be consistent with UK practice ♦ RWE sources were not comprehensive/robust, leading to uncertainty in the benefits of the treatment compared with relevant comparators
TA855	Flatiron German Chart Review	Pooled Flatiron and chart review data used in IPTW in base case	♦ Generalisability: not all treatments in blended comparator applicable to UK clinical practice ♦ Inconsistencies between RWD mix of treatments and company's blended comparator ♦ Limited patient numbers
TA883	RE-MIND2	Direct comparator efficacy (PFS and OS)	♦ RWE analyses for pola-BR were criticised for lacking clinical validity, and were not aligned with previous appraisal estimates
TA886	Flatiron	Late mBC>Death TPs for the CDK4/6 inhibitor arm	♦ N/A
TA898	Flatiron	IPTW used to inform equal efficacy assumption	♦ Small, heterogenous datasets meaning serious risk of bias ♦ Preference for use of comparator trial data

Abbreviations: CDF: Cancer Drugs Fund; **CDK:** cyclin-dependent kinase; **EAG:** External Assessment Group; **FAD:** final appraisal document; **HTA:** health technology assessment; **IPTW:** inverse probability of treatment weighting; **mBC:** metastatic breast cancer; **N/A:** not applicable; **NCRAS:** National Cancer Registration and Analysis Service; **NHS:** National Health Service; **NICE:** National Institute for Health and Care Excellence; **OS**: overall survival; **PFS:** progression-free survival; **PHE:** Public Health England; **pola-BR:** polatuzumab vedotin, bendamustine and rituximab; **PSWA:** propensity score weighting analysis; **RWD:** real-world data; **RWE:** real-world evidence; **SACT:** Systemic Anti-Cancer Therapy; **TPs:** transition probabilities; **UK:** United Kingdom; **US:** United States.

References: [1]IQVIA. Impact of RWE on HTA Decision-making. Available at: https://www.iqvia.com/insights/the-iqvia-institute/reports/impact-of-rwe-on-hta-decision-making [Last accessed: 21.09.23]; [2]Zou D *et al.* EE321 Use of Single-Arm Trials in NICE Reviews of Oncology Drugs. Value in Health. 2022;25(12):S117; [3]National Institute for Health and Care Excellence. NICE real-world evidence framework. Available at: https://www.nice.org.uk/corporate/ecd9/chapter/overview [Last accessed: 20.09.23]; [4]National Institute for Health and Care Excellence. Use of a real-world data external control arm. Available at: https://indepth.nice.org.uk/use-of-a-real-world-data-external-control-arm/index.html [Last accessed: 20.09.23].
Acknowledgements: The authors thank Amie Ennew, Costello Medical, for graphic design assistance. We also thank Matt Griffiths for his review and editorial assistance in the preparation of this poster.

Presented at ISPOR Europe 2023 | Copenhagen, Denmark | 12–15 November 2023