Influence of NICE Real-World Evidence Framework on HTA Submissions: Sensitivity Analyses in Real-World External Control Arm Studies

Putnam Inizio Advisory

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HTA201

Background

- Increasing reliance on **single-arm trials (SATs)** has accelerated the use of **real-world external control arms (RW-ECAs)** in HTA submissions.
- Concerns about **residual confounding** and **unmeasured bias** often limit the acceptability of RW-ECA evidence.
- In July 2023, The **National Institute for Health and Care Excellence (NICE)** real-world evidence (RWE) framework recommends **sensitivity analyses**, including **quantitative bias analysis (QBA)**, to explore this uncertainty (1).

Objective

- This study evaluates whether publication of the framework has corresponded with greater adoption of QBA methods and sensitivity analyses in NICE submissions using RW-ECAs.

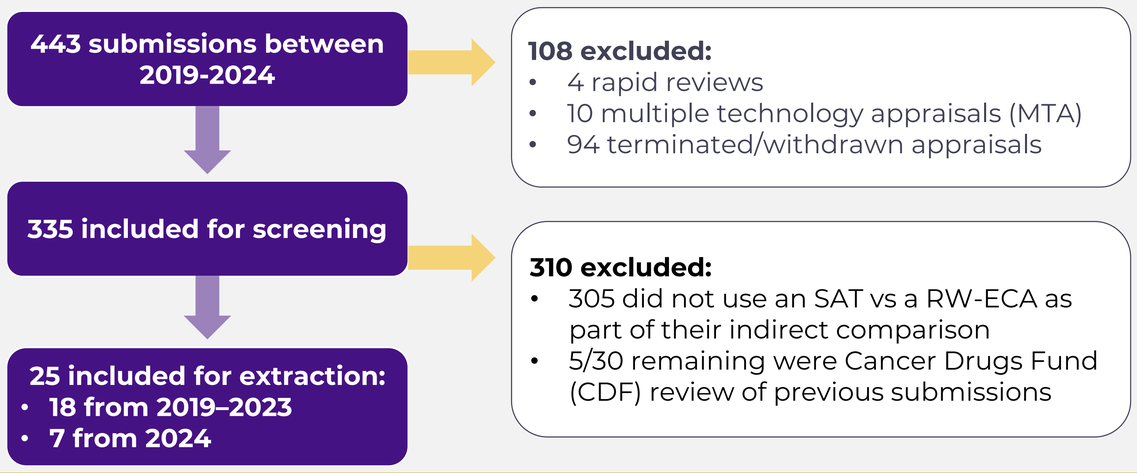
Methods

- **RW-ECAs** submitted to **NICE** were identified through screening company submissions of all single technology appraisals (STAs) with draft guidance from Jan 2019–Dec 2024.
- Submissions that were rapid reviews, multiple technology appraisals (MTAs) or terminated were not included.
- Submissions were included where the company used a **single-arm trial (SAT)** for the intervention and a RW-ECA as a comparator in the **indirect treatment comparison** section.
- Information on the use of **sensitivity analyses**, including **QBA**, to address **residual uncertainty**, and payers' views on their use were extracted.
- This information was compared across two periods, prior to likely adoption of framework (2019–2023); and likely post-framework adoption (2024).

Results

- **Figure 1** shows how many submissions were screened and then included for data extraction, along with reasons for exclusion.
- In total, **25 submissions** with indirect treatment comparison evidence including a company SAT vs a RW-ECA were extracted, with **18 prior** to likely adoption of framework (2019–2023); and **7 likely post-framework adoption** (2024).

Figure 1. Identification of HTA submissions to NICE



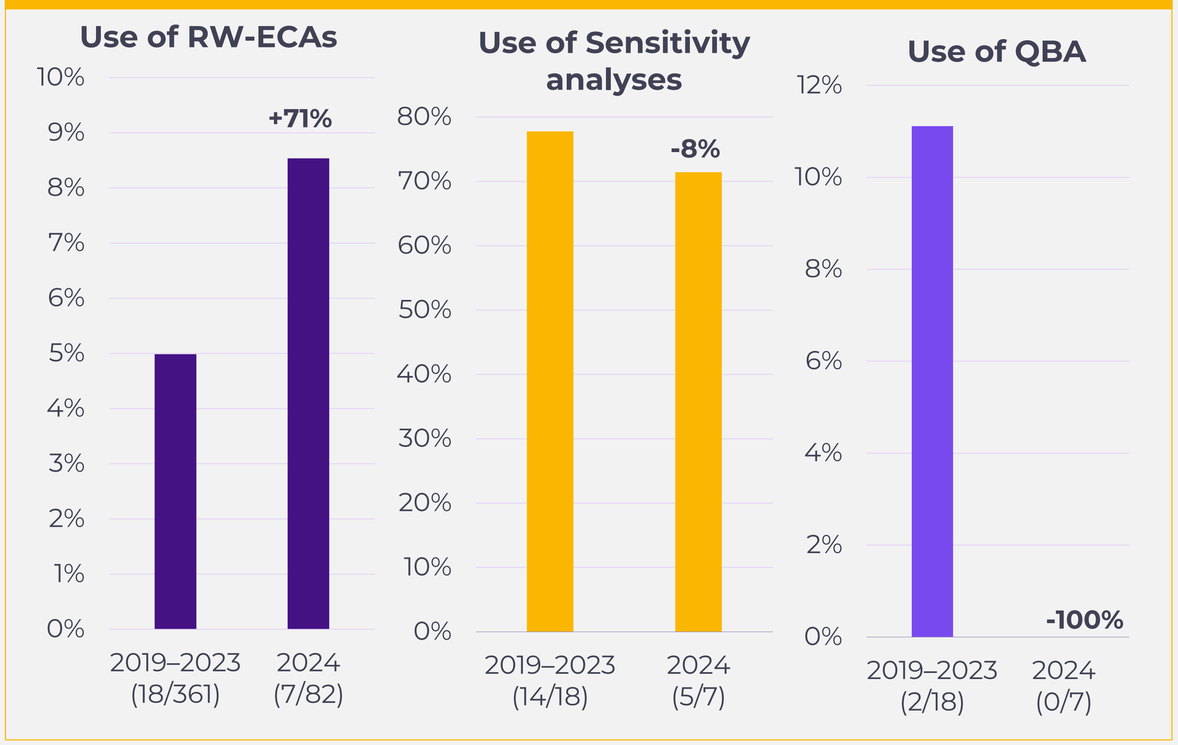
Use of sensitivity analyses, including QBA

- In most cases, companies acknowledged residual confounding without formally quantifying its impact.
- 2 submissions included approaches to assess residual bias. Both used **QBA** (TA812, TA779). Where QBA was used, it was typically limited in scope and lacked structured methodology. None used **negative controls.**
- 19 submissions included sensitivity analyses to explore the impact of different approaches to adjusting for observed sources of bias (e.g. population definitions, data curation decisions, analysis methods, model specification).

Impact of the NICE RWE framework

- **Figure 2** shows a modest rise in the use of RW-ECAs in NICE submissions, increasing from 5.0% in 2019–2023 to 8.5% in 2024.
- However, this expansion was not accompanied by wider uptake of QBA, which remained rare across both periods.
- Most submissions did include some form of sensitivity analysis to explore residual uncertainty, but only a minority went further by addressing it explicitly, suggesting that while uncertainty is often acknowledged, more robust analytical approaches such as QBA have yet to be routinely adopted.

Figure 2. Impact of NICE RWE Framework



Evidence Review Group (ERG) feedback on the approaches used to assess residual uncertainty

Examples include:

- No major concerns with residual bias where sensitivity analyses were conducted, such as balanced baseline characteristics across prior therapy subsets (TA893) and use of inverse probability weighting with a large Flatiron dataset (TA812).
- No explicit comments on residual bias in several submissions despite RW-ECA use (TA789, TA781, TA760).
- Methodological issues raised in individual cases, such as naïve comparisons with inconsistent outcome definitions (TA985), reliance on unverifiable assumptions in unanchored MAICs with limited covariate matching (TA947), or very low effective sample sizes with poor overlap (TA970).

Common themes across submissions:

- Residual confounding highlighted as a persistent concern in 7 submissions (TA947, TA704, TA604, TA1011, TA1001, TA1000, TA954).
- Differences in covariate distributions between SATs and RW-ECAs (e.g. ECOG performance status imbalances) raised in 2 submissions (TA779, TA954).
- Concerns about inadequate adjustment for confounding and selection bias in unanchored designs reported in 5 submissions (TA1011, TA1001, TA1000, TA954, TA1005).

Discussion & Conclusion

- Despite **NICE's updated RWE framework** recommending **sensitivity analyses**, including **QBA**, to address uncertainty in **RW-ECA** evidence, QBA remains largely absent from submissions after one year of likely post-framework adoption, possibly reflecting challenges such as methodological complexity, data limitations, or lack of familiarity among submitters.
- Only one year of post-framework data is included, limiting the ability to draw definitive conclusions on long-term adoption patterns. Uptake may likely increase as the framework becomes more established and embedded in practice.
- There is a clear opportunity for companies to strengthen the **robustness and acceptability** of RW-ECA evidence by systematically incorporating QBA and other sensitivity analyses to address residual bias.

References
1. National Institute for Health and Care Excellence. Real-world evidence framework. Updated January 2025. https://www.nice.org.uk/corporate/ecd9/chapter/overview

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