Leveraging Real-world Data vs. External Trials to Inform Comparative Efficacy within Single-arm Trial-based NICE Submissions

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Background

- Single-arm trials (SATs) have increasingly been used to support oncology appraisals by health technology assessment (HTA) bodies, driven by the ethical and practical challenges of conducting randomized controlled trials (RCTs) involving patients with specialized treatment needs.
- In the absence of direct comparative data in SATs, evidence may be obtained from external clinical trials and/or real-world data (RWD) to inform indirect treatment comparisons (ITCs).
- In consideration of the available external comparator data, statistical approaches including matching-adjusted indirect comparisons (MAIC), simulated treatment comparison (STC), or propensity score matching (PSM) may be employed.
- Currently, there are no explicit HTA guidelines for generating comparative evidence for SAT-based submissions.

Objectives

This study reviewed the acceptance of RWD vs. external trials to inform comparative efficacy in SAT-based HTA submissions.

Methods

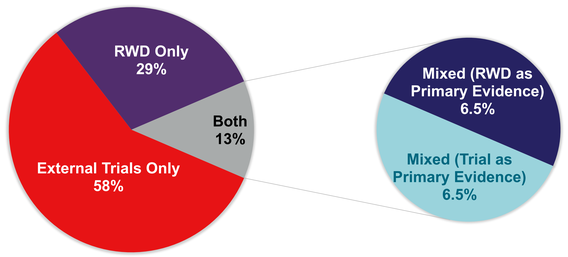
- Oncology SAT-based appraisals from the National Institute for Health and Care Excellence (NICE) between May 2017 and May 2022 were reviewed.
- Full-text screening of committee papers and technology appraisal guidance was conducted by a single investigator, and the extracted data were validated by a second investigator.
- The review focused on identification of the ITC approach used to derive comparative efficacy and the related committee commentaries.

Results

- Of the 31 submissions reviewed, 58% (18/31) used external trials only to derive comparative efficacy, 29% (9/31) used RWD only, and 13% (4/31) used both, with the variance driven by external data availability, limitations, and relevance (**Figure 1**). Half of these sources were deemed fit-for-purpose by the committee.

Results (cont.)

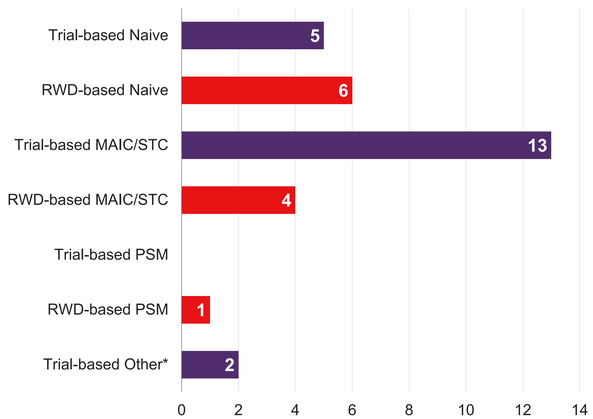
Figure 1. Type of Evidence Used in NICE Submissions



Abbreviation: NICE = National Institute for Health and Care Excellence; RWD = real-world data

- Of all submissions, around one-third (11 of 31) obtained individual patient-level data for the external control arm. MAIC/STC was the most commonly used method (13 of 20) when external trial data was the primary source, while naive analysis was most frequently applied to RWD (six of 11) (**Figure 2**).

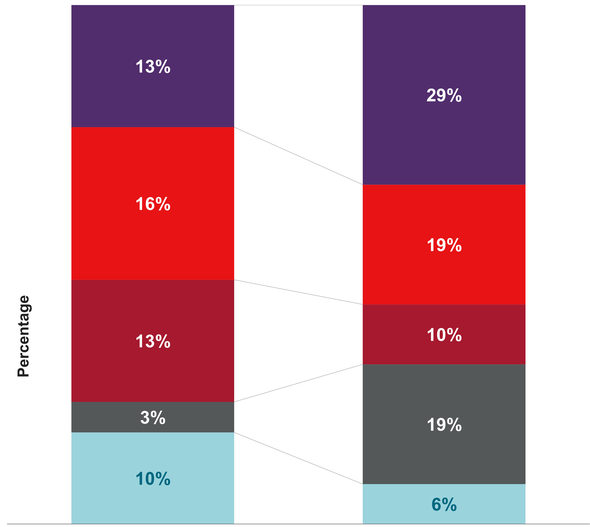
Figure 2. ITC Methods—RWD vs. External Trials for Comparators



Abbreviation: MAIC = matching-adjusted indirect comparison; PSM = propensity-score matching; RWD = real-world data; STC = simulated treatment comparison
*Note: Both submissions with other ITC approaches used single-arm trials as the primary source, with one constructing the comparator arm from its own trial and the other submission from landmark analysis.

- Among the 13 submissions leveraging RWD, more than 60% (n=8) were accepted as valid evidence,[1-8] benefiting from the ability to mitigate uncertainty due to lack of direct comparison by allowing precise matching and covariate adjustment.
- Overall, criticisms of SAT-based submissions were primarily due to data limitations (42%) and insufficient comparability (35%). Other concerns included limited generalizability of the results (23%), inadequate covariate adjustments (23%), and inappropriate statistical methods (16%) (**Figure 3**).

Figure 3. Criticism on Quality of Evidence: RWD vs. External Trials



- Data Limitations: High uncertainty due to limitation of the evidence (e.g., small sample size, data immaturity, short follow-up)
- Insufficient Comparability: Lack of comparability vs. trial population or insufficient adjustment of population difference
- Limited Generalizability of the Results: Results not generalizable to the marketing authorization population
- Inadequate Covariate Adjustments: Limited information or insufficient adjustment to covariates in ITC analyses
- Inappropriate Statistical Methods: Insufficient justification/rationale for method selection (e.g., lack of sensitivity analysis using alternative method)

Abbreviations: ITC = indirect treatment comparison; RWD = real-world data

- In particular, the committee emphasized that unanchored MAIC does not effectively reduce uncertainty or bias, often favoring supplementation with naive analyses as benchmarks (52%, 16/31).
- Submissions using external trials as primary evidence were mainly criticized for lack of comparability with trial population and insufficient adjustments of population difference, followed by concerns about result generalizability to the market-authorized population.
- In contrast, RWD-based submissions were criticized for high uncertainty due to data limitations (e.g., small sample size, immaturity, short follow-up), followed by insufficient covariate adjustments in ITC analyses and lack of comparability to trial populations.

Conclusions

RWD has been increasingly used as an alternative to suboptimal trials for external control in SAT-based HTA submissions, offering more granularity and flexibility. HTA consensus on its appropriateness for external control remains low, with key discussions on whether the data are fit-for-purpose and the adequacy of covariate adjustments.

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Disclosures

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