Transporting evidence across borders: A targeted review of the use and acceptability of non-local data to derive real-world external control arms in submissions to NICE

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Background and objective

- Real-world external control arms (RW-ECAs) are an increasingly common source of comparative evidence in HTA submissions (1)
- Limitations in the quality/quantity of local data in some countries often necessitate reliance on non-local data to derive RW-ECAs (2)
- HTA agencies prefer local data, citing concerns that important effect modifiers differ between countries (3-5). Transportability is defined as the degree to which studies using non-local data can estimate unbiased treatment effects in local populations (2)
- This study reviews current practices in the use of non-local data to derive RW-ECAs and their acceptance in HTA

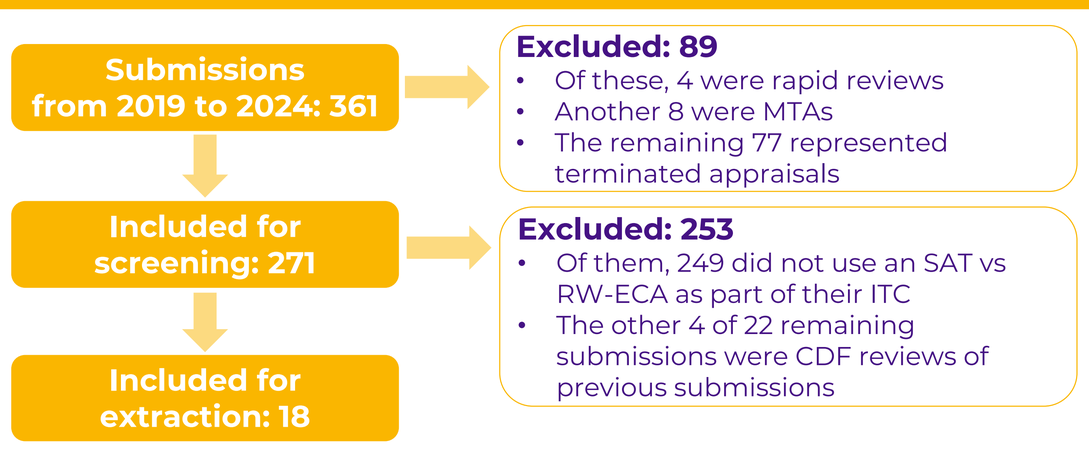
Methods

- RW-ECAs submitted to NICE were identified through screening company submissions of all single technology appraisals with draft guidance from January 2019 to December 2023
- Submissions were excluded if they were rapid reviews, MTAs, or terminated appraisals
- Submissions where the company used an SAT for the intervention arm and an RW-ECA for the comparator in an ITC were included
- Information on justifications for using non-local data, evidence presented to support transportability, and payers' views on limitations of non-local data were extracted

Results

The search yielded 361 submissions, of which 18 included ITC evidence comparing a company SAT with a RW-ECA **(Figure 1)**

Figure 1. Identification of HTA submissions to NICE



Disease areas

Of the 18 submissions included, 16 were for oncology indications, plus 1 each for cardiovascular conditions and rare diseases (advanced systemic mastocytosis).

Use of non-UK data and justification

- Three of 18 submissions derived their RW-ECA from UK data only, and 4/18 used UK data along with non-UK data. Of these, 2 derived RW-ECA using both UK and non-UK data, 1 used UK data for some outcomes but non-UK data for others, and 1 used US data for the primary analysis and UK data in a sensitivity analysis
- Of the 12 submissions justifying use of non-UK data, justifications included larger sample size, and availability of relevant outcomes, confounders, and/or variables to identify the indication **(Table 1)**
- Amongst submissions using some non-UK data, 8 used data from the United States, 8 from Europe, 3 from Asia, and 2 from Israel

Table 1. Justifications provided for the use of non-UK data

Justification	Number of submissions
Larger sample size	3
Reported outcomes of interest	2
Studies used are of higher quality	1
Larger numbers of baseline characteristics available	1
Longer follow-up time	1
Unable to identify specific indications in UK data	1
Availability of key study variables	1
Only available evidence	1
Identified in the SLR informing the submission	1

Suitability and transportability of non-UK data

The majority of submissions provided no verbal arguments or empirical data to support the suitability and/or transportability of non-UK RWD used **(Table 2)**.

Table 2. Support for suitability and/or transportability of non-UK RWD

- Five of 15 (33%) submissions included verbal arguments to support suitability of non-UK RWD
  - ➢ Four submissions argued that the standard of care, testing protocols, and populations and outcomes were similar between the UK and the relevant study country, supported by clinical expert opinion in 3 submissions
  - ➢ One submission claimed that the data source was suitable because it had been used in a previous submission
- Four of 15 (27%) submissions provided empirical evidence to support transportability of non-local data
  - ➢ Two submissions used comparator data from the UK in a sensitivity analysis for ITC or scenario analysis for a cost-effectiveness model
  - ➢ Two submissions compared patient/disease characteristics between the study sample and an external UK data source
- No studies applied methods to reweight/adjust data to increase transportability, and none used formal transportability analysis to adjust the RW-ECAs to increase comparability of the study sample to the UK population

ERG feedback

The feedback provided by ERGs on the use of non-UK data confirmed their preference for local data and often criticised submissions for using non-UK data not reflective of the UK clinical practice **(Table 3)**.

Table 3. ERG feedback regarding the use of non-UK data

Feedback	Number of submissions
Non-UK data not reflective of UK clinical practice	5
Compared with the UK clinical practice, RW-ECAs could have better outcomes because of treatments included	2
Non-UK data provided a more appropriate comparison (as specific disease mutations were identifiable)	1
Larger sample size of non-UK data justifies its use, but a more systematic approach should be used for identifying and selecting an appropriate data source	1
UK comparative results should be presented fully	1

Reimbursement vs transportability

- Of 18 submissions, 7 (39%) were fully reimbursed, 6 (33%) were conditionally reimbursed via the CDF, and 5 (28%) were not reimbursed
  - ➢ Of 3 submissions using UK data alone, 1 (33%) was fully reimbursed, 1 (33%) was funded via the CDF, and 1 (33%) was not reimbursed
  - ➢ Of 4 submissions using UK and non-UK data, 2 (50%) were fully reimbursed, 1 (33%) was funded via the CDF, and 1 (33%) was not reimbursed
  - ➢ Of 11 submissions using non-UK data alone, 4 (36%) were fully reimbursed, 4 (36%) were funded via the CDF, and 3 (27%) were not reimbursed
- Mixed evidence on whether providing additional information to support transportability increased the likelihood of reimbursement
  - ➢ Half of the submissions using more formal approaches to support transportability (e.g., using UK comparator data for sensitivity analysis, assessing differences in characteristics) were not reimbursed

Conclusions

- Concerns about transportability of non-local data are regularly expressed by NICE
- Although the updated NICE RWE framework recommends empirical methods to assess/correct the lack of transportability of non-local data, these methods have not previously been used in practice (4)
- Increased confidence in RW-ECA evidence could be achieved through improved quality/accessibility of UK data and use of best-practice methods where non-local data are used

Abbreviations: CDF, Cancer Drugs Fund; ECA, external control arm; ERG, Evidence Review Group; HTA, health technology assessment; ITC, indirect treatment comparison; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; RWD, real-world data; RW-ECA, real-world external control arm; SAT, single-arm trial; SLR, systematic literature review; UK, United Kingdom

References
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