Presented at the Professional Society for Health Economics and Outcomes Research (ISPOR) Europe; November 15th, 2023; Copenhagen, Denmark

HTA315

Implications for Rare Diseases: NICE Guidance and Outcomes on Implementing Bayesian Borrowing Approaches for External Control Data

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Objectives

To analyze submissions to the National Institute for Health and Care Excellence (NICE) using external control arms (ECAs) and Bayesian dynamic borrowing (BDB) methods and inform the need for optimising the quality of such evidence for future HTA submissions

Key Findings

Use of ECAs in recent HTA submissions has been frequent, but BDB is uncommon. The recent NICE Real-World Evidence (RWE) framework contains guidance on BDB, indicating acceptability in future HTA submissions

BACKGROUND

- In rare diseases, 'gold-standard' randomised controlled trials (RCTs) can be challenging or infeasible to conduct due to ethical concerns and small patient sample sizes
- As such, using **historical data to form an ECA** can allow patients to receive the intervention treatment, while enhancing sample sizes in clinical trials to potentially expedite access
- As the NICE RWE framework has shown, incorporating historical data into trials can be achieved through static or dynamic borrowing methods, both of which can be applied in a frequentist or Bayesian framework
- **Static borrowing** methods borrow fixed, pre-specified amounts of historical data, often through matching algorithms, such as propensity score matching
- **Dynamic borrowing** methods, such as BDB, control the amount of borrowing based on how commensurable the historical data are to the current trial data

METHODS

All existing NICE highly specialised technology (HST) guidance, as well as technical appraisal (TA) guidance published from December 2016–May 2023, were reviewed

- Submissions were classified as assessing 'clinical effectiveness with RCT' (RCT) or 'clinical effectiveness without RCT' (non-RCT), **according to the data used to inform comparative clinical effectiveness**
- Non-RCT data appraisals were further analysed for ECA usage and subsequently which data borrowing method was applied
- Appraisal data were independently checked by a secondary researcher

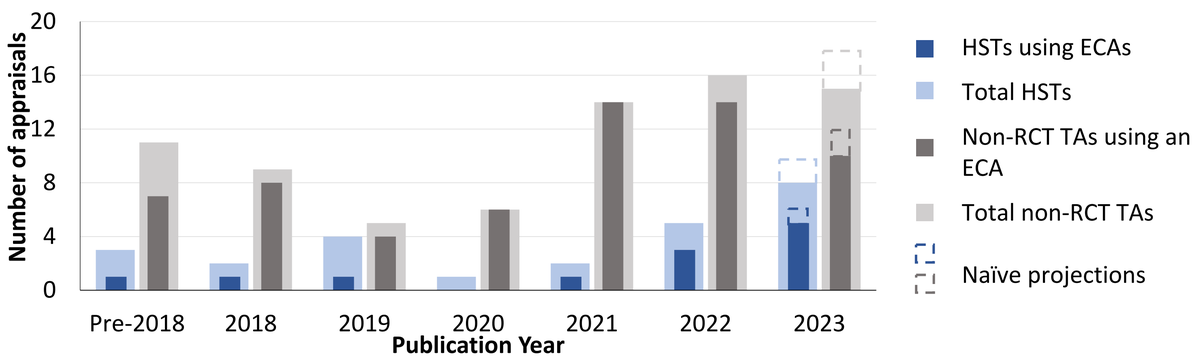
Using the NICE Real-World Evidence (RWE) framework[1], potential implications were identified for future submissions using ECAs and dynamic borrowing methods, such as BDB

RESULTS: NICE APPRAISAL REVIEW

In total, 23 HSTs have been appraised by NICE within this review period and made publicly available. 369 individual technology appraisals (TAs) were appraised during the review period

- **Use of non-RCT data was less common in TAs**: 18% (*n*=68/369) of the TA submissions used non-RCT data to assess comparative clinical effectiveness, compared with 70% (*n*=16/23) of HSTs
- **In appraisals without RCTs, ECAs were common**, occurring in 82% (*n*=56/68) of the TAs and 75% (*n*=12/16) of HST submissions
- Use of ECAs in NICE submissions has increased in both TAs and HSTs (Figure 1)

Figure 1. Frequency of ECA usage in HSTs and non-RCT TAs[a]



No HSTs, and only 2 TAs, involved use of BDB methods

- The only examples of BDB included **Bayesian hierarchical models (BHMs)** proposed by an evidence review group (ERG) to **borrow data in a basket trial context** for two oncology appraisals: TA630 and TA644 (Table 1)
- The BHM framework allowed data to be borrowed across baskets, which were stratified by tumour type. This accounted for heterogeneity in response across baskets, to derive overall response rates across all tumour types

Table 1. NICE committee conclusions on the proposed BHM approaches in TA630 and TA644

Appraisal	Conclusions from the NICE committee
TA630 Larotrectinib	• The BHM was a **'useful tool for exploring heterogeneity'** and **'should be considered as part of decision making'**[5]
TA644 Entrectinib	• The BHM was a 'reasonable alternative', but **other modelling approaches should be explored as more data is currently being collected**[6] • Also, experts from multiple external stakeholders were '**unsure on how to best capture heterogeneity** in the absence of large numbers of patients'[7]

Table 2. HSTs using ECAs and Non-RCT TAs using an ECA

Topic	HSTs (*n*=12)	Non-RCT TAs (*n*=56)
ECA data sources	Elicited from natural history studies in all cases (*n*=12)	Sources varied, consisting typically of arms from other randomised trials, other forms of non-randomised evidence, or both in *n*=45 cases (81%)
ECA data with patient matching methods	*n*=6 appraisals (50%)	*n*=39 appraisals (70%)
Matching methods	*n*=4 (67%) of the appraisals in the row above used propensity score matching or propensity score weighting via inverse probability weighting (IPW)[b]	*n*=32 (65%) of the appraisals in the row above used propensity score matching or propensity score weighting via IPW

- ECA data sources differed among HSTs and TAs; however, methods to match patients from external data to current trial data overlapped (Table 2)

RESULTS: IDENTIFICATION OF GUIDANCE

The NICE RWE framework[1] contains guidance on using RWE to form ECAs, focusing on assessment of data suitability and transparency in reporting biases

- ECAs can be formed from **RWE data** and data from **previous trials**. The use of external data to **augment concurrent controls** within an RCT is also permitted
- ECA studies should aim for **target trial emulation**[c], although this is difficult when using RWD; data must be adapted to **minimise differences between the ECA and intervention arm**, including patient characteristics and treatment setting. **Pocock's six criteria**[8] are cited, which assess the exchangeability[d] between the ECA and internal trial arm and inform on biases present if the criteria are not met
- **Sensitivity analysis and quantitative bias analysis** are recommended to assess risk of biases

The RWE framework acknowledges the existence of methods that place different weight on external data

- Guidance on data borrowing methods in the RWE framework is taken from the **CHTE2020 sources and synthesis of evidence report**[2]
- In the report, Bayesian methods[e] are described in the context of synthesising randomised and non-randomised evidence
- The RWE framework also references **Gray, C.M. *et al***[3], which proposes a four-step process for assessing the evidence of studies using external data derived from RWE. Within it, BDB is suggested to combine evidence from **exchangeable historical data and internal controls**

POTENTIAL IMPLICATIONS FOR FUTURE HTA SUBMISSIONS

When incorporating ECAs into the clinical evidence base, consider clarity of evidence, through use of quality assessment tools and bias reporting methods, in line with the NICE RWE framework[1]

- **Prospective quality assessment of ECA data sources** could be attempted, using the *Data Suitability Assessment Tool (DataSAT)*[1] or the *ArRoWS critical appraisal tool*[9], with the latter being a pragmatic choice for assessment of RWE studies
- **ECA data sources could be transparent and baseline data sources could be provided at submission**. ERGs could be able to reproduce synthesised sources of ECA data and verify comparisons between intervention and ECAs to enhance validity
- **Qualitative reporting on minimising the risk of bias** could be conducted using the template in Appendix 2 of the RWE framework
- **Quantitative bias analysis** can be particularly important when using RWE ECA data, with even 'simple' methods (such as the e-value approach[1]) being useful for decision-makers to assess the impact of biases on results

If BDB is used, consider sensitivity analyses on method choice and prior distribution specification

- This could include implications of each type of method on **type 1 error and statistical power**, to provide NICE with metrics for comparison. A clinical trial simulation study could help to achieve this

CONCLUSIONS

- **ECAs are common in submissions that use non-RCT data**. For accepted and published HSTs, ECAs consisted of **natural history data in all cases**
- However, **dynamic borrowing methods are uncommon**, despite having the potential to flexibly incorporate relevant external data
- **Most submissions that incorporated ECAs used static borrowing methods**, rather than dynamic borrowing. Potentially, this is either due to available data not permitting statistically robust dynamic borrowing, or uncertainty in how NICE would view the strength of this evidence
- The recent **NICE RWE framework[1]** provides guidance on, and quality assessment templates for, ECA data. It also contains guidance on dynamic borrowing methods, which are well complemented by other suggested approaches, such as target trial emulation and QBA
- These findings indicate that **dynamic borrowing methods could become more common in future submissions**, particularly in rare diseases with noteworthy burden. This is supported by an increase in NICE's capacity for evaluations by 2023–24[4]

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NOTES

[a] Data for the graph was collected up to October 2023
[b] IPW utilizes propensity scores to adjust for confounders by balancing covariates across treatment groups
[c] Designing non-randomised studies to mimic the hypothetical randomised trial that would be carried out with no constraints on ethics or feasibility[1]
[d] Exchangeability of groups is, broadly speaking, how comparable they are. Group A and Group B are fully exchangeable with respect to outcome measure X, if X remains the same given identical exposure history between A and B[3]
[e] Such as the modified power prior, commensurate prior, and hierarchical modelling

ACKNOWLEDGMENTS & DISCLOSURES

- External validation support was provided by Prof. Richard Grieve, PhD, of London School of Hygiene and Tropical Medicine, and was funded by Sarepta Therapeutics, Inc
- This study was funded by Sarepta Therapeutics, Inc. **AC** and **JI** are employees of Sarepta Therapeutics, Inc. **MG**, **JS** and **DW** are employees of Wickenstones Ltd, and served as consultants to Sarepta Therapeutics, Inc for the duration of this research