HTA264

Baseline natural history models in network meta-analysis: guidance versus implementation in National Health and Care Excellence (NICE) appraisals

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INTRODUCTION

- Cost-effectiveness analyses often rely on a baseline model (BM) representing absolute natural history under a "standard treatment" in the comparator set, and a model for relative treatment effects (RTE).
  - Estimates from the two models are then combined to obtain the disease course under the new treatment.
- NICE Decision Support Unit Technical Specification Document (TSD) 5 describes evidence synthesis issues relating to the construction of BMs.[1]
  - Further, the guidance recommends independent construction of BMs following the same modelling framework used for RTE synthesis and describes how the two models are integrated to generate absolute effects for each treatment.
  - Of focus in this study, the guidance highlights the importance of using population-specific evidence in BMs and the need for sufficiently detailed reporting justifying the evidence used.

Key recommendations for sources of evidence for baseline outcomes[1,2]

- An independent systematic literature review (SLR) to identify evidence for the baseline (or reference) intervention should be performed.
- Evidence should represent, as specifically as possible, the population of interest.
  - Ideally, this is informed by a large observational study conducted in the target population.
  - Alternatively, this may include evidence from recent trials, relevant cohort studies, register studies, or expert opinion.
  - Pooling evidence for the reference treatment from the same trials included in the network meta-analysis (NMA) of RTEs is only appropriate if these studies' populations are representative of the target population and under current circumstances.
    - This is particularly true in situations where the evidence base contains outdated trials with different standards of care, study design, and/or very selective study eligibility criteria.
    - The rationale should be justified in each case.
    - Researchers should consider whether all (or only a subset of) trials should be used to inform baseline outcomes.

OBJECTIVES

- This study explores reported implementation of BMs alongside models for RTEs in NMAs supporting NICE technology appraisals (TAs), focusing on their use, and if used, the evidence used to populate the BMs and evidence review group (ERG)/external assessment group (EAG) opinion on applicability to the UK population.

METHODS

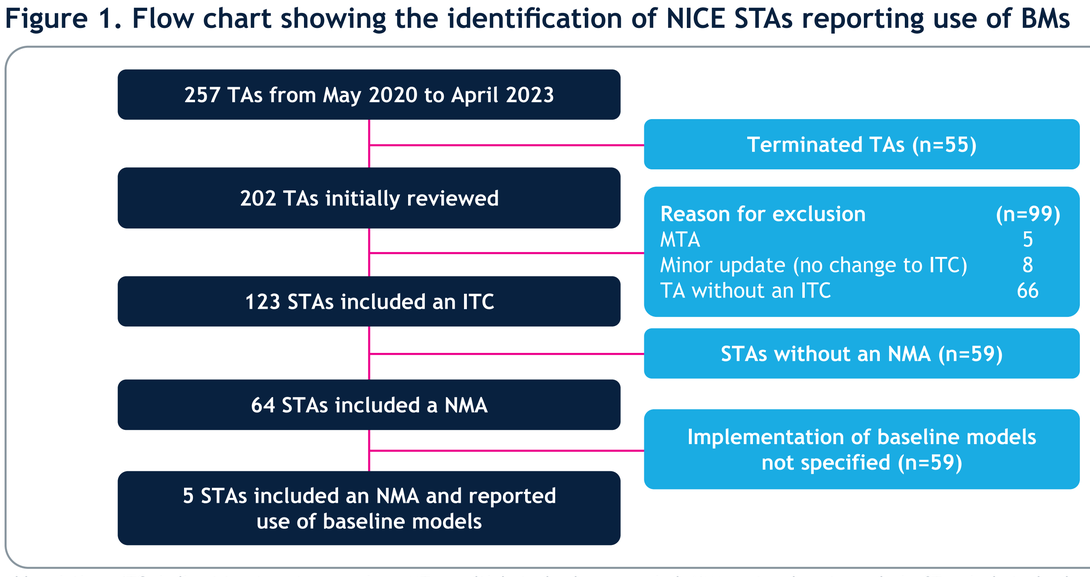
- TAs posted on the NICE website between May 2020 and April 2023 were considered.
  - Multiple technology appraisals (MTAs); TAs with changes to marketing authorisation, recommendation updates, or revised patient access schemes, rather than resubmissions; and TAs without a supporting indirect treatment comparison (ITC) were all excluded.
- Information describing implementation of BMs was extracted, where reported, from publicly available NICE committee papers which include company submission (CS) summaries, clarifications questions and company responses, and ERG/EAG reports.

RESULTS

Targeted literature review results

- Of the 257 TAs, 64 included an NMA in the CS (Figure 1).
  - In most (92.2%), the implementation of BMs was not specified in published materials.

Figure 1. Flow chart showing the identification of NICE STAs reporting use of BMs



Abbreviations: ITC, indirect treatment comparison; MTA, multiple technology appraisal; NMA, network meta-analysis; STA, single technology appraisal; TA, technology appraisal.

Implementation of Baseline Natural History Models

- Only 5 TAs reported the use of BMs. A summary of the available information regarding implementation of BMs for each identified TA is presented in Table 1.
  - Information on the evidence source for BMs was limited, with only 2 TAs[3,4] reporting sufficient detail to determine that they implemented a meta-analysis including all reference arms from all trials included in RTE models.
    - Justification for choice of evidence was not reported in the published materials.
  - Only 1 TA[4] was criticised for not selecting evidence reflective of UK clinical practice.
- TA828[4] provided the most robust assessment of BM implementation, where the ERG noted several criticisms:
  - "The sources for the baseline risk…in the CS are the placebo arms, where they exist, of exactly the same set of trials used to estimate relative treatment effects. This runs contrary to TSD5…"
  - "The studies informing the baseline model in the CS have not undergone a separate search process oriented to the baseline setting…"
  - "…there has been no filtering of these studies towards the baseline setting. The ERG noted there is high variability in baseline characteristics across placebo arms of included trials... [which] may weaken external validity: it may be that only a subset of these trials will match the decision problem population, or even none at all..."

Table 1. Summary of BM Implementation in NICE STAs

NICE STA	Disease area	Reported evidence source for BMs				Additional detail
		Independent SLR conducted?	Targeted to population of interest?	Specified evidence used?	Justification for choice provided?	
TA861[5]	axSpA	?	?	✗	✗	BM methods and assumptions in (unavailable) CS Appendix EAG considered that the analytic approach described and all assumptions made, were appropriate
TA856[3]	UC	?	?	✓	✗	NICE clarification questions indicated use of BM, no further detail provided
TA828[4]	UC	?	✗	✓	✗	Several criticisms ERG recommended selecting sources closest to UK clinical practice, with most appropriate distribution of effect modifiers Revised base case used a subset of trials to inform BMs ERG noted caution in time-constrained re-analysis, limitations in generalisability, and recommended a protocol-driven SLR per NICE TSD5
TA753[6]	Epilepsy	?	?	✗	✗	Predictive mean and SD from the BM to inform the NMA defined as figure footnotes only ERG noted discrepancy between baseline seizure rate (a key driver of the economic model) in the trials included in the ITC when compared to observational studies from a recently published SLR, thus the former may not reflect clinical practice
TA718[7]	axSpA	?	?	✗	✗	Baseline effect and RTE modelled separately in all analyses ERG considered that the methods used to conduct the NMAs were appropriate

Abbreviations: axSpA, axial spondyloarthritis; BM, baseline model; CS, company submission; EAG, external assessment group; ERG, evidence review group; NMA, network meta-analysis; RTE, relative treatment effects; SD, standard deviation; SLR, systematic literature review; UC, ulcerative colitis.

CONCLUSIONS

- Besides the limited time horizon, the primary limitation of this study is that it relies on the publicly available information from NICE TAs, and thus more CSs may have made use of BMs or provided additional information, which was impossible to identify due to redaction or unavailable appendices.
- Despite recommendations for transparency, reporting of the evidence informing BMs remains unclear across NICE TAs, thereby hindering assessment of the suitability of the BMs for the decision problem and population of interest.
- Manufacturers are advised to ensure that key assumptions and methods used to implement an NMA, including the use of BMs, are clearly documented and reproducible.
  - In particular, justification for the evidence source(s) included in BMs should be provided.
- There is a need for a consistent approach in the evaluation of such methods by NICE ERG/EAGs, and standardised reporting of feedback and critique.
  - Of the 64 TAs identified which included an NMA, the NICE ERG/EAG review provided critique on the implementation of BM in only one.
- Manufacturers often conduct an initial NMA that is generalisable globally and adapted to local settings. Based on the findings of this review, NICE ERG/EAG review has not requested a revised NMA using an alternative BM evidence source to date, with only one TA advised to consider sources closest to UK clinical practice.
  - However, should the guidance for BMs to align with the population of interest in the UK setting be more strictly enforced moving forward, manufacturers will need to take care to prepare accordingly ahead of submission.
    - This is particularly relevant if performing an independent SLR in line with NICE TSD5, which may be time and resource intensive depending on indication.
    - Further consideration is needed into the impact of the upcoming launch of the European Network for Health Technology Assessment Joint Clinical Assessment, multiple populations of interest, and ensuring suitability of BMs to each setting.

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