Treatment comparison for HTA. Using NICE as an example, does current use reflect the evolution from anchored methods to complex models, and adjustment techniques?

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MSR133

Background and Objectives

- Assessment of comparative effectiveness is central to health technology assessment (HTA), with reimbursement and access decisions fundamentally dependent on how new treatments perform relative to existing standards of care. For HTA bodies such as the National Institute for Health and Care Excellence (NICE) in England and Wales, robust and transparent comparative evidence is a prerequisite. Submissions are expected to systematically identify the totality of relevant evidence and apply rigorous analytical methodologies to derive credible comparative effectiveness estimates, upon which both clinical and cost-effectiveness determinations are made.[1] The selection and application of these analytical methods is therefore not a peripheral technical consideration; it can be a critical and consequential determinant of appraisal outcomes, influencing whether a treatment is deemed cost-effective, recommended with restrictions, or rejected entirely.
- Historically, direct head-to-head randomised controlled trials (RCTs) provided the gold standard for treatment comparison. However, the realities of modern drug development including fragmented treatment landscapes, small or rare disease populations, accelerated approval pathways, and the proliferation of therapeutic options means that direct comparative evidence is frequently unavailable, incomplete, or not generalisable to the decision population of interest.[2]
- In response, indirect treatment comparison (ITC) methods have evolved considerably. Early approaches, such as naive or unadjusted indirect comparisons, gave way to anchored network meta-analyses (NMA), which synthesise evidence across trials sharing a common comparator, enabling simultaneous comparison of multiple treatments within a connected evidence network. Whilst NMA represents a methodological advancement, its validity rests on the assumption of homogeneity across trials, an assumption that is frequently challenged in practice.[3]
- More recently, the field has moved toward increasingly sophisticated methods designed to address heterogeneity and improve the relevance of comparisons to specific decision contexts.
- Population-adjusted indirect comparisons (PAICs), including matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC), have emerged as techniques to align patient populations across trials in the absence of head-to-head data. MAIC reweights individual patient data (IPD) from one trial to match the aggregate baseline characteristics of a comparator trial population, whilst STC uses regression modelling on IPD to predict outcomes in a target population. Both methods, however, are limited by their reliance on the availability of IPD from at least one trial and their inability to simultaneously synthesise evidence across broader treatment networks.[4]
- To address these limitations, multilevel network meta-regression (ML-NMR) has emerged as a more flexible and statistically robust extension of conventional NMA. ML-NMR integrates IPD and aggregate data simultaneously within a network meta-analytic framework, enabling covariate adjustment across multiple trials and treatments at the individual patient level. This approach preserves the breadth of a connected evidence network whilst accounting for effect modification and population heterogeneity.[5]
- Beyond these approaches, component NMA has been applied in settings where treatments comprise multiple combinable components. Use of Bayesian NMA with informative priors has also gained traction, particularly in small or sparse networks where incorporating prior evidence can stabilise estimates. More recently, meta-regression techniques incorporating continuous or categorical effect modifiers have been used to explore and partially account for cross-trial heterogeneity, improving the interpretability and decision-relevance of comparative estimates in heterogeneous evidence bases.[6]
- We sought to describe and critique the comparative treatment effectiveness approaches observed across NICE appraisals, examining whether current practice reflects the full breadth of methodological evolution available.

Methods

- Given the descriptive and exploratory nature of the research objective, scoping review methodology was used to map the approaches used for comparative effectiveness assessment across recent NICE technology appraisals.
- The review was restricted to final appraisal documents published by NICE for single technology appraisals (STAs) and highly specialised technology appraisals (HSTs) between 1st January 2025 and 31st March 2026. With the time window selected to allow us to understand contemporary HTA practice.
- Terminated appraisals were excluded.
- Final appraisal documents, technology appraisal guidance, and associated evidence review group (ERG) reports were retrieved directly from the NICE website.
- A standardised data extraction framework was developed to capture relevant information across all included appraisals. For each appraisal, the following were extracted: the primary method(s) used to assess comparative effectiveness (e.g., direct RCT evidence, NMA, MAIC, STC, ML-NMR, external control arms, or observational data); the availability and use of individual patient data (IPD); and any specific critique, concern, or endorsement of these methods documented by the ERG or NICE Appraisal Committee.
- Data were extracted by a single experienced reviewer and independently verified by a second reviewer to ensure accuracy and minimise the risk of extraction error. Any discrepancies identified during verification were resolved through discussion and consensus.
- Both quantitative and narrative description of findings are provided.

Conclusions

- The continued use of conservative approaches likely reflects a rational response to the current HTA environment in which there is somewhat limited precedent for the acceptance of findings derived from complex methodologies. And, in which use of more sophisticated methods may introduce additional assumptions and layers of uncertainty that, rather than strengthening a submission, invite greater scrutiny and complexity in communicating.
- Submissions face a recurring and continued nature of critique regarding method selection handling of heterogeneity and effect modifier adjustment suggesting challenges reflecting the inherent complexity of generating robust comparative evidence in the absence of head-to-head trial data.
- Newer meta-analytic methods and population adjustment techniques when rigorously applied have the potential to directly address many of these criticisms, reducing bias, improving population relevance, and ultimately strengthening the demonstration of therapeutic value to decision-makers.
- In addition, justification of method selection, demonstration of sensitivity to analytical choices, and transparent acknowledgement of uncertainty are becoming prerequisites for credible submission.
- Findings from this review demonstrate that NICE submissions have evolved from binary evidence (trial-based or not) to approaches incorporating layered methodological complexity. For pharmaceutical companies, this necessitates strategic planning of evidence generation from early development stages.
- Going forward, success in market access will depend not merely on evidence quantity but on evidence strategy and the deliberate architecture of comparative effectiveness assessment through a plurality of methodologically-appropriate techniques.

Results

- A total of 127 technology appraisals were published by NICE between 1st January 2025 and 31st March 2026, of which 30 were terminated and therefore excluded from analysis, yielding an evaluable sample of 97 appraisals (Figure 1).
- Most of the included reports were single TAs (N=92, 95%) with only five of the reports identified being HSTs (N=5, %).
- Most of the appraisals addressed cancer/ haematology (N=44) with neurology (N=9), rare genetic disorders (N=9), with additional evaluations covering allergy, dermatology, endocrine/metabolic disease, hematology, immunology, nephrology, respiratory, rheumatology, transplant or women's health (N=35) (Figure 2).

Figure 1. PRISMA flowchart depicting disposition of included reports

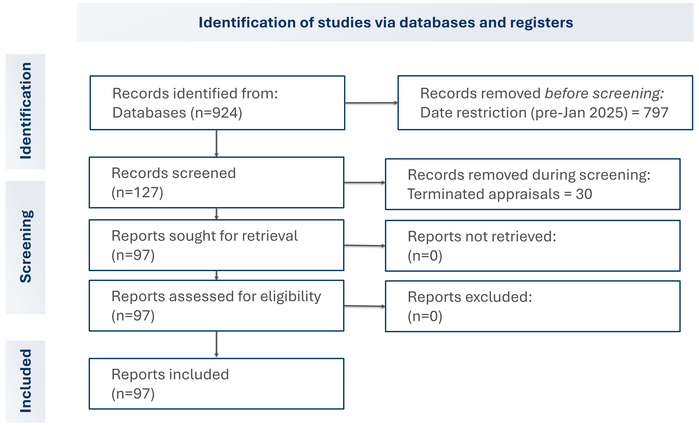
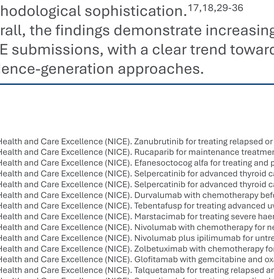


Figure 2. Distribution of included reports by condition



- The majority (n=67) reported the use of direct head-to-head randomised controlled trial evidence or standard NMA as the primary method for comparative effectiveness assessment (Figure 3). The continued reliance on direct RCT evidence and standard NMA approaches underscores their value and place within the gold-standard evidence hierarchy. These methods seem to remain preferred when feasible, but their limitations in addressing heterogeneity, cross-trial variation, and increasingly complex patient populations were continuously critiqued.
- The use of PAIC methods was common-place with MAIC used in almost a fifth of submissions in our dataset(n=19). MAIC seemed to be used as the standard approach for addressing cross-trial heterogeneity and baseline covariate imbalance, functioning as a pragmatic bridge between traditional meta-analysis and real-world observational data.[7-25] In our data set there is no pattern of method use by indication, with most MAIC (n=15) seen in oncology submissions likely reflecting the underlying distribution. Use of STC approaches were identified less frequently and were found in use independently or alongside MAIC analyses.[7,13,19] The frequent combination of MAIC with STC, NMA, and real-world evidence could suggest a growing trend towards triangulating approaches, when no single methodology is considered definitive.[7,13,17-19] This pattern likely reflects recognition that decision-making requires methodological pluralism to explore uncertainty rather than reliance on a single approach.
- Advanced NMA methodologies were also seen in use, including non-proportional hazards NMAs using for example cubic spline modelling and ML-NMR. [27-29] These methods were typically applied in situations where survival outcomes violated proportional hazards assumptions or where treatment-effect modifiers differed substantially across studies. From our dataset it seems such methods are being selectively adopted where standard methods are inappropriate.
- There is integration of real-world evidence, from supplementing immature trial data to constructing external comparator cohorts for single-arm studies seemingly showing a fundamental shift in the traditional evidence hierarchy. RWE looks to be increasingly integral to comparative effectiveness assessment. The parallel use of propensity score matching, inverse probability weighting, and multivariable adjustment indicates industry-wide development of technical capacity for RWE integration, likely driven by recognition that payers now expect such methodological sophistication.[17,18,29-36]
- Overall, the findings demonstrate increasing methodological complexity within NICE submissions, with a clear trend toward population-adjusted and hybrid evidence-generation approaches.

Figure 3. Overview of methods identified within included reports

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19. National Institute for Health and Care Excellence (NICE). Zanubrutinib for treating relapsed or refractory mantle cell lymphoma. Technology appraisal guidance [TA1081]. London: NICE; 2025
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