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How similar is similar enough? Assessment of indirect treatment comparisons to support similarity for NICE's cost comparison route

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Background

The National Institute for Health and Care Excellence (NICE) is turning to cost comparison (CC) analysis to cope with growing demand. CC requires the demonstration of *similar or improved* effectiveness and safety between the intervention and relevant comparator(s).[1]

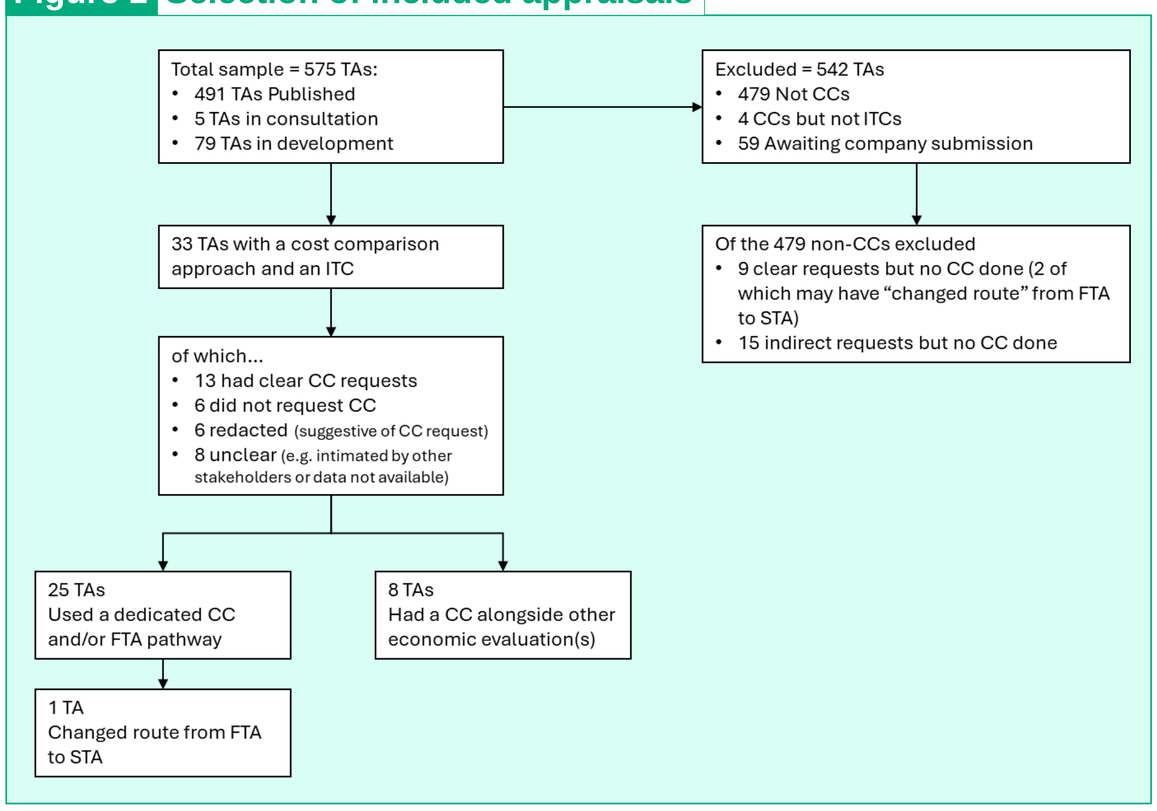
When a head-to-head (H2H) study is not available, demonstration of similar effectiveness must be performed via indirect treatment comparison (ITC). The definition of similarity in an ITC has been explored.[2-4] However, there is no guidance on how these methods might be applied in HTA. Our review asked:

1. What methods are available to determine whether two treatments have similar health benefits when no H2H evidence is available?
2. What methods are available to determine whether a new treatment is non-inferior to a comparator when no H2H trial has been conducted?
3. What are the key considerations considered by EAGs and NICE to determine whether a CC route is appropriate?
4. How can information on the likelihood of similarity of health effects be best presented to inform decision making?

Methods

We searched Embase, MEDLINE and the International HTA Database for methods studies and case studies. We also identified NICE technology appraisals – in development or published between 1 Jan 2017 and 5 Feb 2024 – where similarity had been claimed through an ITC. Searches were registered on PROSPERO.[5]

Figure 1 Selection of included appraisals



Abbreviations: CC, cost comparison; FTA, fast track appraisal; ITC, indirect treatment comparison; STA, single technology appraisal; TA, technology appraisal

Figure 2 Barriers and facilitators to having a CC analysis accepted by committee

Facilitators

- CC is complemented by one or more other economic evaluations ***(TA773, TA931)***
- Clinical experts state that assumption of equivalence is reasonable or that the intervention is likely to provide clinically meaningful benefits ***(TA861, TA849, TA829, TA820, TA799, TA916)***
- H2H trial(s) against a similar comparator shows equivalence ***(TA820, TA799)***
- Uncertainty is acknowledged but likely to be in favour of the intervention ***(TA861, TA829, TA456)***

Barriers

- Assertion of noninferiority confuses a lack of statistically significant difference with non-inferiority ***(TA931, TA849)***
- Wide CIs are presented as evidence of similarity, rather than a measure of uncertainty ***(TA670, TA799)***
- There is a lack of long-term data for efficacy and/or safety outcomes ***(TA829, TA456)***
- The NMA focusses on a population different to the scoped population ***(TA820, TA799)***
- The NMA contains a small number of trials and/or is missing data for key subgroups ***(TA918, TA849, TA829, TA773)***
- There are differences in baseline characteristics and/or outcomes are measured at different timepoints between trials, or other heterogeneity between trials in the NMA ***(TA861, TA820, TA773, TA456)***
- The NMA offers up markedly variable results for different outcomes (e.g. OS and PFS) ***(TA849)***
- Clinical experts state that assumption of equivalence is unreasonable or that the intervention is unlikely to provide clinically meaningful benefits ***(TA849)***
- Dosage used or other aspects of the included trials in the NMA are not relevant to the NHS ***(TA799)***

Abbreviations: CC, cost comparison; CI, confidence (or credible) interval; H2H, head-to-head; NHS, National Health Service; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

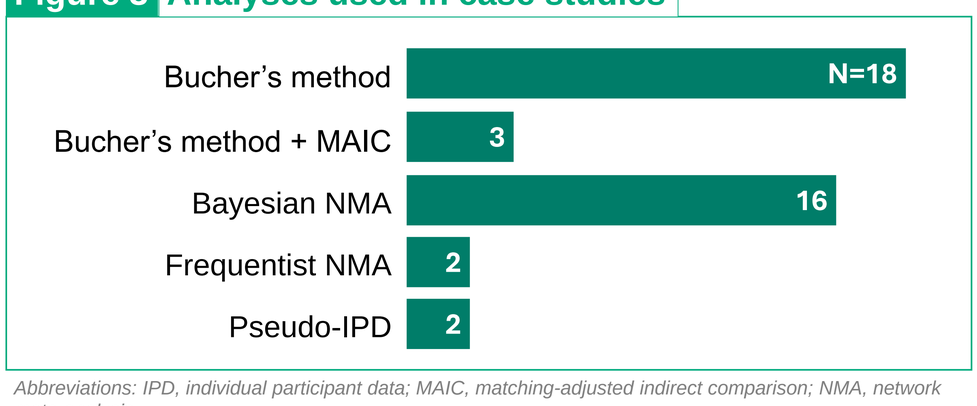
Results (methods studies and case studies)

We identified five methods papers from which three key approaches to determining equivalence emerged:

1. Bayesian approaches to quantifying the likelihood of equivalence
2. Incorporation of a non-inferiority margin
3. Consistency with historical data

A total of 41 case studies were identified where an assessment of similarity or non-inferiority was an aim of the analysis. The analyses that case studies used are shown in **Figure 3**.

Figure 3 Analyses used in case studies



Abbreviations: IPD, individual participant data; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Results (previous NICE appraisals)

We identified 491 TAs published between 1 Jan 2017 and 5 Feb 2024. A further five were in consultation, and 272 in development. Of these, 33 appraisals were identified that used CC based on an ITC **(Figure 1)**.

There were nine instances where the company suggested or intimated that a CC may be applicable, but ultimately for which a CC was not performed

None of the appraisals applied any of the methods we identified from the literature. Instead, companies used narrative summaries to assert similarity, often based on a lack of statistically significant differences – this often led to committees expressing uncertainty about the results.

Where uncertainty was expressed, committees were either reassured or concerned by the presence of absence of certain arguments **(Figure 2)**.

Conclusions

- Formal methods to assess equivalence in ITC-based cost comparison are emerging but have not yet been applied in practice.
- The most promising method is the estimation of non-inferiority indirect treatment comparisons in a Bayesian framework followed by a probabilistic comparison of the indirectly estimated treatment effect against a pre-specified non-inferiority margin.

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References: **1.** NICE health technology evaluations: the manual. NICE process and methods [PMG36]. London: NICE; 2022 [updated 31 Oct 2023]. **2.** Uhlmann L, et al. Hypothesis testing in Bayesian network meta-analysis. BMC Med Res Methodol. 2018;18(1):128. **3.** Lin J, et al. Non-inferiority and networks: Inferring efficacy from a web of data. Pharm Stat. 2016;15(1):54-67. **4.** Lehert P, Szoeke C. Comparison of modafinil and pitolisant in narcolepsy: a non-inferiority meta-analytical approach. Drugs Context. 2020;9. **5.** Allen A, et al. Review of methods used to determine similarity of effectiveness and safety when indirect treatment comparison is required. PROSPERO 2024 CRD42024512814.