Simulated treatment comparisons in NICE technology appraisals: Frequency, trends, and implications

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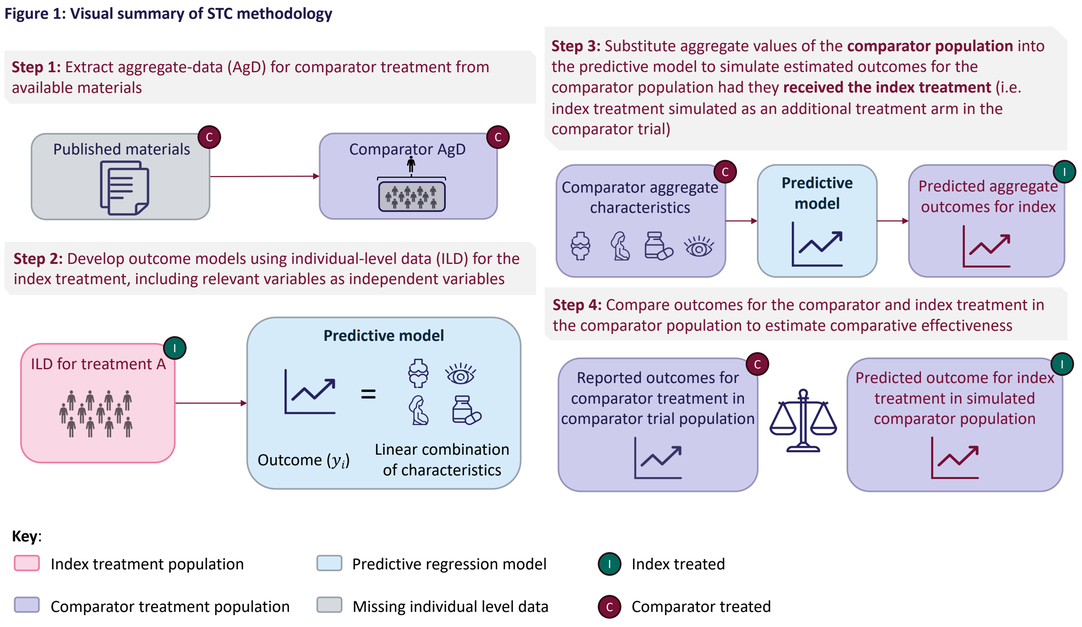
Introduction

In health technology assessment (HTA), indirect treatment comparisons (ITCs) are required when direct head-to-head trials between treatments are unavailable. Simulated treatment comparison (STC) is an ITC methodology that estimates outcomes in a comparator population, accounting for treatment effect modifiers and prognostic variables (1,2). When a common comparator is available, an anchored STC can be used; where it is not available, an unanchored STC can be used, though this requires stronger assumptions about the comparability of patient populations. A visual summary of the methodological steps in STC is shown in Figure 1.

In 2020, the National Institute for Health and Care Excellence (NICE) Decision Support Unit published an update to Technical Support Document (TSD) 18, which discouraged the use of matching-adjusted indirect comparisons (MAICs) in favour of STC for anchored and, under strict assumptions, unanchored comparisons (2,3). A previous review of submissions from April 2020 to June 2023 identified 36 submissions including MAICs (11.1/year), and 4 including STCs (1.2/year) (4). Of those including STCs, 3 were in an unanchored setting, 1 was in an anchored setting, and none formed the ITC base case.

Figure 1: Visual summary of STC methodology



Objectives

- **To understand whether STC adoption has increased over the last 2 years**
- **To identify potential reasons for STC implementation in practice**

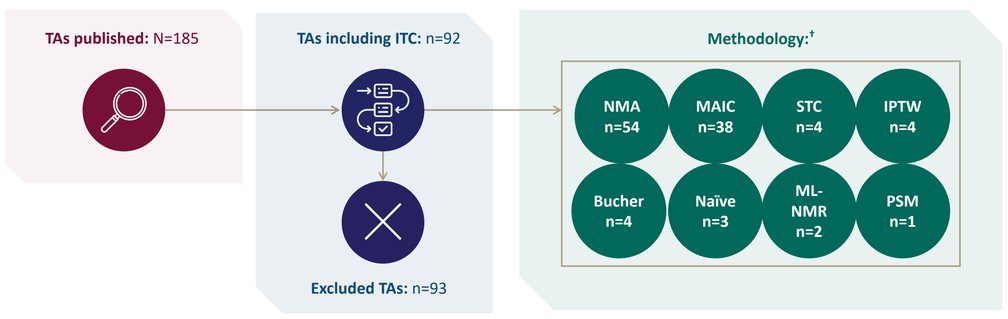
Methods

NICE technology appraisal (TA) guidance committee papers published between 7th June 2023 and 4th June 2025 were reviewed. Documents associated with each TA were examined to identify those that included ITC(s). The frequency of STC and MAIC use was then determined, as well as whether these were anchored or unanchored.

Submissions that either did not include/mention an ITC, or were terminated, unclear, or an update to a previous submission prior to 7th June 2023 were excluded.

In addition to exploring utilisation in submissions, a targeted literature search was conducted to identify any recent methodological developments for STC application, which may help to improve utilisation in HTA.

Figure 2: Review outputs

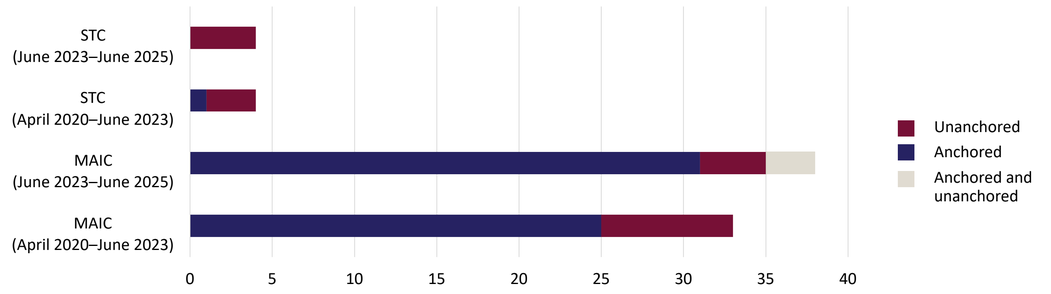


† Submissions often included more than one type of ITC.

Results

Since 7th June 2023, 185 TAs have been published. The previous review identified 36 MAICs and 4 STCs over a 3-year period compared with 38 MAICs and 4 STCs over a 2-year period in this current review (Figure 2). All four STC submissions were unanchored and also included a MAIC (Figure 3).

Figure 3: MAIC versus STC uptake in NICE TAs



In two submissions, STC was used in the base case ITC (TA1020, TA1021); the remaining two were conducted as a sensitivity or secondary analysis (TA970, TA986). In TA1020, STCs and MAICs were performed on all comparators, with no preference stated by the company. Similarly, in TA986, both MAIC and STC were used in a secondary analysis to NMA in the base case, although no clear reasoning was given for this in the committee papers. In both TA970 and TA1021, STCs were implemented instead of MAIC in the primary or secondary analyses due to poor overlap between the populations in terms of key patient characteristics.

Table 1: Submissions including STC between April 2020–June 2023 and June 2023–June 2025

Review	TA number	Treatment	Indication	Anchored or unanchored STC	Base case ITC	MAIC also conducted?
April 2020–June 2023	TA880	Tezepelumab	Severe asthma	Anchored	NMA	No
	TA833	Zanubrutinib	Waldenstrom's macroglobulinaemia	Unanchored	MAIC	Yes
	TA802	Cemiplimab	Advanced cutaneous squamous cell carcinoma	Unanchored	Naïve comparison	Yes
	TA756	Fedratinib	Myelofibrosis	Unanchored	MAIC	Yes
June 2023–June 2025	TA970	Selinexor with dexamethasone	Multiple myeloma	Unanchored	MAIC	Yes
	TA986	Lebrikizumab	Atopic dermatitis	Unanchored	NMA	Yes
	TA1020	Eplontersen	Hereditary transthyretin-related amyloidosis	Unanchored	MAIC and STC	Yes
	TA1021	Crizotinib	Non-small cell lung cancer	Unanchored	STC	Yes

Discussion

The results demonstrate increased use of MAIC and STC, from 11.1/year to 19.0/year for MAIC, and 1.2/year to 2.0/year for STC. The most common rationale for use of STC instead of MAIC was to address poor overlap and low effective sample size (TA970, TA1021). In addition, STC was used as the base case ITC method for the first time in two submissions, indicating growing preference for STC. However, STC was typically presented as a complementary (TA1020) or secondary (TA970, TA986) analysis alongside MAIC, suggesting a reluctance to present STC alone. Similarly, an external assessment group expressed a slight preference for MAIC (TA1020), despite both methods being presented. Thus, despite increased STC use and NICE TSD 18 guidance, MAIC appears to remain the preferred approach.

Since 7th June 2023, several methodological advancements have been published. Zhang et al (2024) (5) gave a recap of the single imputation method proposed by Ishak et al (2015) (6), which involves simulating patient characteristics using observed correlations and distributional assumptions, and predicting outcomes in the simulated population using design equations. The multiple imputation approach was then proposed, which involves taking multiple bootstrap samples of the simulated dataset and reconducting the analysis multiple times, using a sample size aligned with that of the comparator trial. Additionally, Zhang et al (2024) (5) introduced an infinite population approach, which applies STC to an extremely large simulated population (5). Ren et al (2024) (7) proposed an unanchored approach that utilises standardisation and the NORmal To Anything (NORTA) algorithm to enable the estimation of marginal treatment effects without aggregation bias.

Conclusion

Despite the updated guidance favouring STCs over MAICs, the application of STCs in NICE TAs remains limited, with only a modest increase in its use observed over the past 2 years. The persistent preference for MAIC in practice indicates a notable disconnect between the evolving methodological recommendations and their real-world implementation. As such, improved understanding of the methodological benefits, practical challenges, and barriers to use of STCs is needed to support and promote adoption of STC . Recent methodological developments in STC, such as the standardisation-based approach developed by Ren et al (2024) (7), may help to improve the uptake of STC in the future.

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Abbreviations

AgD, aggregate-level data
HTA, health technology assessment
ILD, individual-level data
IPTW, inverse probability of treatment weighting
ITC, indirect treatment comparison
MAIC, matching-adjusted indirect comparison
ML-NMR, multi-level network meta-regression
NICE, National Institute for Health and Care Excellence
NMA, network meta-analysis
NORTA, NORmal To Anything
PSM, propensity score matching
STC, simulated treatment comparison
TA, technology appraisal
TSD, Technical Support Document