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# Simulated Treatment Comparison or Matching-Adjusted Indirect Comparison: which wins in the battle for prominence and validity in population-adjusted indirect treatment comparison?

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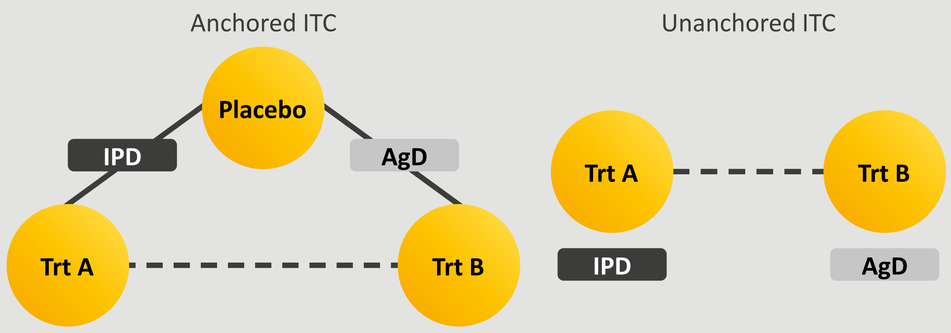
## Objective

To compare published guidance for population-adjusted indirect treatment comparison (ITC) methods and investigate recent use of these methods – particularly the application of simulated treatment comparisons (STC) with no common comparator, in submissions to the UK's National Institute for Health and Care Excellence (NICE)

## Background

- STC and matching-adjusted indirect comparison (MAIC) are methods for conducting pairwise population-adjusted ITC that adjust for imbalances in baseline characteristics between study populations
- Pairwise population-adjusted ITCs utilise individual patient-level data (IPD) from an intervention study and published aggregate data (AgD) for a comparator study. They can be conducted through a common comparator such as placebo (anchored ITC) or with no common comparator (unanchored ITC) **[Figure 1]**

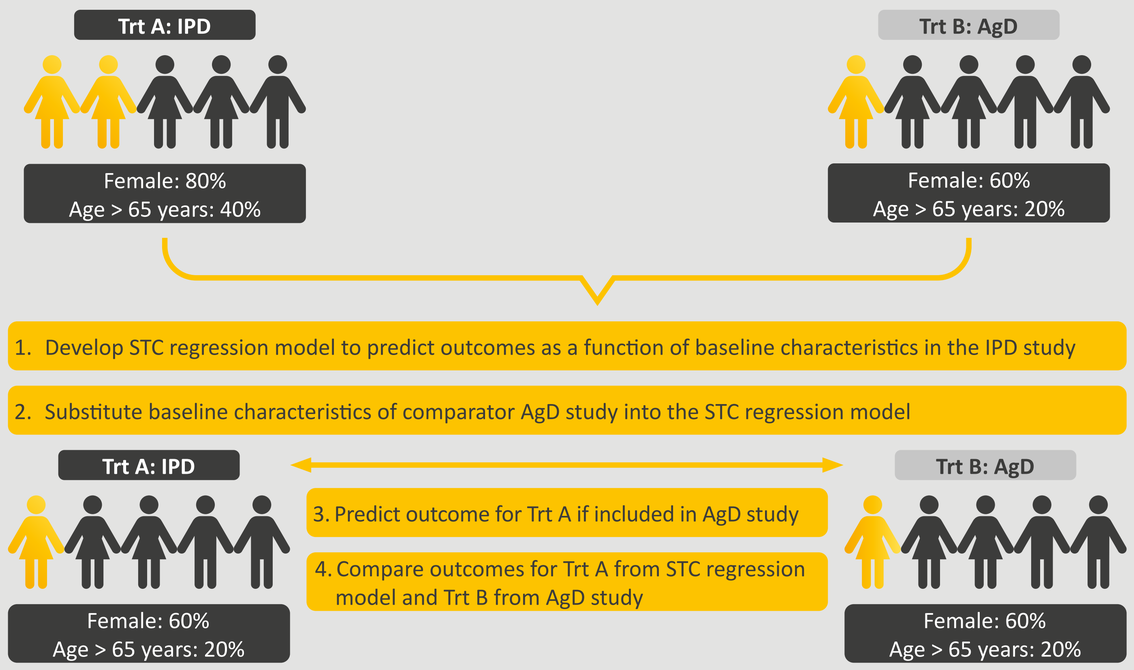
**Figure 1: Diagram of anchored and unanchored ITCs**




**Note:** Solid line represents direct evidence and dotted line represents the ITC.
**Abbreviations:** AgD, aggregate data; IPD, individual patient-level data; ITC, indirect treatment comparison; Trt, treatment.

- NICE Decision Support Unit (DSU) Technical Support Document 18[1] outlines both STC and MAIC methodologies, however, subsequent guidance in 2020 from NICE's DSU recommended that "MAICs should not be used under any circumstances"[2]
- STC is also not without its limitations, particularly when using non-linear models. An overview of STC methodology is shown in **Figure 2**
- Multi-level network meta-regression (ML-NMR) is the newest population adjustment method[3]. However, there is little guidance around implementing the method in time-to-event scenarios and currently minimal utilisation of the method in NICE submissions

**Figure 2: Overview of STC methodology**




**Abbreviations:** AgD, aggregate data; IPD, individual patient-level data; STC, simulated treatment comparison; Trt, treatment.

## Methods

- Published guidance and methods for unanchored and anchored STCs and MAICs were reviewed, as were key publications from simulation studies, testing method performance
- Additionally, NICE submissions following the DSU guidance in 2020 were examined to quantify the use of STCs and their acceptance as evidence (searches performed on 7th June 2023)

## Results

- Identified evidence regarding the most appropriate choice of STC or MAIC in the case of an anchored population-adjusted ITC was conflicting
- Phillipo et al. 2020 reviewed the performance of STCs, MAICs and ML-NMR in an anchored simulation study. MAICs performed poorly in all simulation scenarios, and in some cases increased the bias compared with a standard ITC[4]. In contrast, from the simulation study conducted by Remiro-Azócar et al. 2021, the authors concluded that MAIC provides the most accurate estimates, with STC leading to greater bias[5]
- Unanchored MAICs have been also tested in a simulation study[6], however there are far fewer publications reporting implementation of STC in the unanchored scenario and no simulation study testing performance of the method was identified

**Table 1: Summary of STCs used in submissions to NICE in 2020 or later**

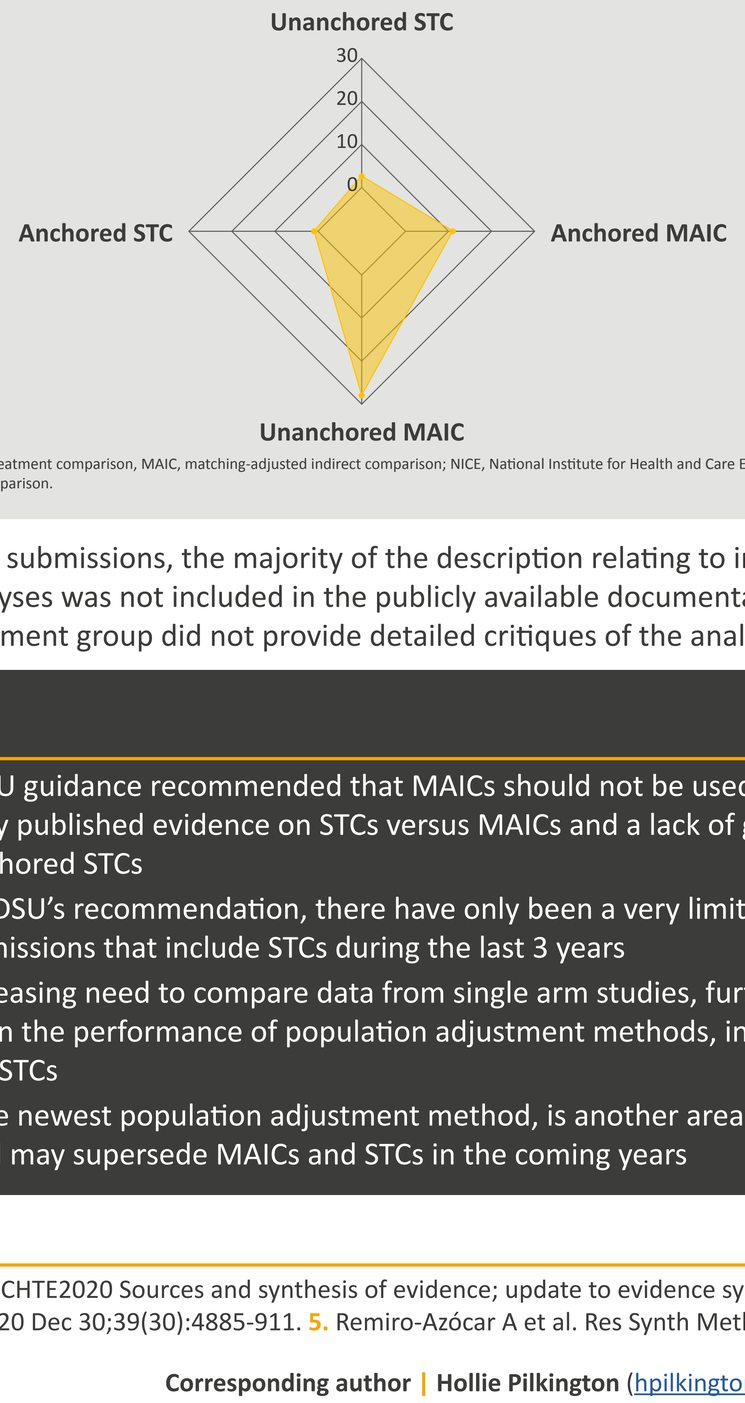
| Appraisal number | Treatment | Indication | Date of publication | Anchored or unanchored? | Base case ITC | MAIC also conducted? |
|---|---|---|---|---|---|---|
| TA880 | Tezepelumab | Severe asthma | Apr 2023 | Anchored | NMA | No |
| TA833 | Zanubrutinib | Waldenstrom's macroglobulinaemia | Oct 2022 | Unanchored | MAIC | Yes |
| TA802 | Cemiplimab | Advanced cutaneous squamous cell carcinoma | Jun 2022 | Unanchored | Naïve comparison | Yes |
| TA756 | Fedratinib | Myelofibrosis | Dec 2021 | Unanchored | MAIC | Yes |

**Abbreviations:** ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; STC, simulated treatment comparison.

Since the 2020 DSU recommendations were published (and up to 7th June 2023), there were only **4 STCs** submitted to NICE, of which **3** were **unanchored** comparisons and none formed the ITC base case **[Table 1]**

In comparison, there were **36 MAICs** submitted to NICE during the same time period, of which **25** were **unanchored**, **8** were **anchored** and **3** submissions reported **both** anchored and unanchored comparisons **[Figure 3]**

**Figure 3: Radar plot of number of population-adjusted ITCs used in submissions to NICE in 2020 or later**




**Abbreviations:** ITC, indirect treatment comparison, MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; STC, simulated treatment comparison.

- For all four STC submissions, the majority of the description relating to implementation of the STC analyses was not included in the publicly available documentation and the external assessment group did not provide detailed critiques of the analyses

## Conclusions

- Although DSU guidance recommended that MAICs should not be used, there is contradictory published evidence on STCs versus MAICs and a lack of guidance about unanchored STCs
- Despite the DSU's recommendation, there have only been a very limited number of NICE submissions that include STCs during the last 3 years
- With an increasing need to compare data from single arm studies, further research is required on the performance of population adjustment methods, in particular unanchored STCs
- ML-NMR, the newest population adjustment method, is another area for further research and may supersede MAICs and STCs in the coming years

## References

1. Phillippo DM et al. NICE DSU Technical Support Document 18 2016. Available from http://www.nicedsu.org.uk 2. Welton NJ et al. CHTE2020 Sources and synthesis of evidence; update to evidence synthesis methods. 2020. 3. Phillippo DM et al. J R Stat Soc Series A: Stat Soc. 2020 Jun;183(3):1189-210. 4. Phillippo DM et al. Statistics in medicine. 2020 Dec 30;39(30):4885-911. 5. Remiro-Azócar A et al. Res Synth Methods. 2021 Nov;12(6):750-775. 6. Hatswell AJ et al. Value Health. 2020 Jun;23(6):751-759.

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