Are we dealing with heterogeneity in network meta-analysis appropriately? A review of NICE submissions

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BACKGROUND

Background: Over the years, advanced methods such as network meta-analysis (NMA) have become integral in the realm of evidence synthesis, which facilitates the simultaneous comparison of multiple interventions across various studies by considering both direct and indirect evidence. Nevertheless, conducting an NMA poses a significant challenge due to the inherent heterogeneity between studies and is the most cited critique of ITC methodologies.[1]

Aim: To understand (i) the causes of heterogeneity in published literature and (ii) how it has been handled in NICE single technology appraisals (STAs) published for non-oncology indications in recent years.

METHODS

- A desk research was conducted to identify the root causes of heterogeneity in the NMA.
- For the second objective, we reviewed the final guidance of STAs published by the NICE in the last 2 years (January 2022-November 2023) for non-oncology indications.
- Terminated, withdrawn and in-development STAs were excluded.

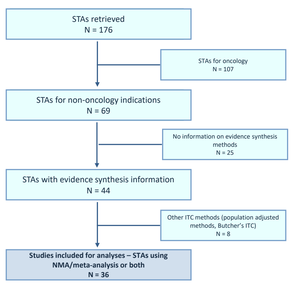

Figure 1: Summary of the inclusion/exclusion of STAs

- A total of 176 STAs were retrieved; 69 of these were non-oncology indications. Information on evidence synthesis methods was reported in 44/69 and out of which NMA, meta-analysis, or both were conducted in 36 STAs. **(Figure 1)**

The heterogeneity in NMA has been addressed poorly in non-oncology studies. Despite the availability of various guidelines or task-force recommendations on conducting NMA, the adherence to these guidelines for addressing heterogeneity is limited.

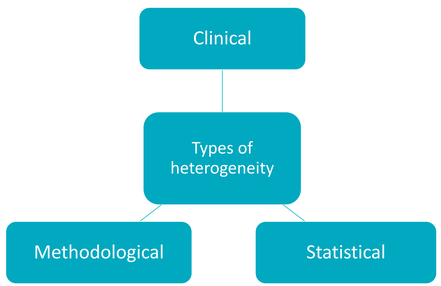

Figure 2: Types of heterogeneity

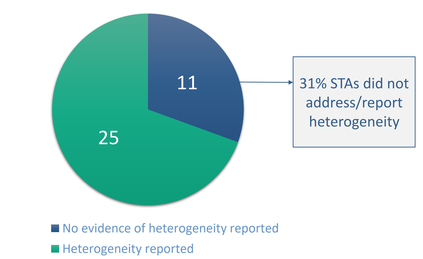

Figure 3: Reporting of heterogeneity in STAs

Abbreviations: MAIC – Matching Adjusted Indirect Comparison; NICE – National Institute for Care and Excellence; STA – Single Technology Appraisal.

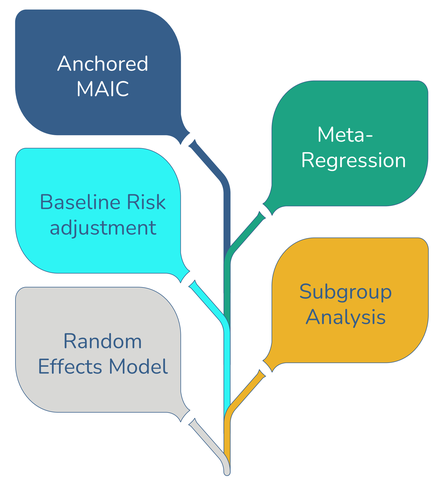

Figure 4: Most common Approaches to deal with heterogeneity

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RESULTS

- The three major types of heterogeneity were identified from the literature, namely clinical, methodological, and statistical heterogeneity **(Figure 2).**
  - The clinical heterogeneity arises due to differences in patient characteristics, study populations, interventions, comparators or outcome measures.
  - Heterogeneity caused by methodological differences between studies is termed as methodological heterogeneity. This includes variations in study design, outcome measurement tools, duration of follow-up etc.
  - Statistical heterogeneity refers to variability in treatment effects beyond what would be expected due to chance alone.
- The root cause of heterogeneity in studies was the existence of interaction between treatment effect and study-level covariates, i.e., the presence of treatment effect modifiers.
- Among the STAs included in the analysis, nearly one-third of submissions did not address or report the evidence of heterogeneity **(Figure 3).**
- The most common approach used to address heterogeneity was the random effects model. Only a very few STAs used methods like subgroup analysis or meta-regression to explain the potential causes of heterogeneity.[2] To explore the impact of adjusting for treatment effect modifiers, a supportive anchored matching-adjusted indirect comparison (MAIC) was only used in one of the STAs **(Figures 4 and 5).**[3]

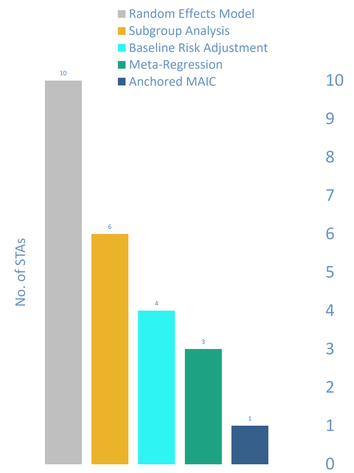

Figure 5: Usage of methods to deal with heterogeneity

Abbreviations: MAIC – Matching Adjusted Indirect Comparison; STA – Single Technology Appraisal.

DISCUSSION

Heterogeneity in evidence synthesis is inevitable. There are methods available to explore or address the heterogeneity. Thus, it is important that heterogeneity is handled appropriately to avoid biased estimates and ensure robust decision-making.

References:

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3. Phillippo, D.M., Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from http://www.nicedsu.org.uk

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