Integrating the Estimand Framework into NMA Feasibility Assessments: Current Practices and Methodological Recommendations

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Background

- The ICH E9(R1) addendum has established the estimand framework as the standard for primary trial design, driving a push to integrate these principles into evidence synthesis.
- Despite theoretical consensus, the literature currently lacks systematic, actionable guidelines for assessing estimand concordance during NMA feasibility assessments.
- This structural disconnect between theory and practice motivated our scoping review to map current methodologies and establish a formal procedural framework for evaluating statistical exchangeability.

Methods

- A scoping review was conducted following JBI methodology to map the extent to which the estimand framework is integrated into feasibility assessments for NMAs.
- Eligibility criteria included human studies in which at least one randomized controlled trial (RCT) was analyzed with other RCTs or non-RCTs.
- Peer-reviewed publications and relevant technical documents reporting on feasibility assessments of NMAs or other ITCs of RCTs were considered.
- Database search was conducted in PubMed, along with a hand search. Keywords included terms such as *"feasibility assessment"*, *"network meta-analysis"*, and *"estimand"* to target publications about estimand framework integration into NMA feasibility assessments.
- Screening was completed by two independent reviewers against eligibility criteria. Data extraction was completed for variables including reported network connectivity, within-trial heterogeneity and cross-trial heterogeneity in a feasibility assessment.

Study Selection & Synthesis Process

- We synthesized methodological guidance documents for the feasibility assessment criteria covering within-study heterogeneity, between-study heterogeneity, and estimands.
- These criteria were applied to extract and characterize current practices in NMA feasibility assessments from the reviewed literature.

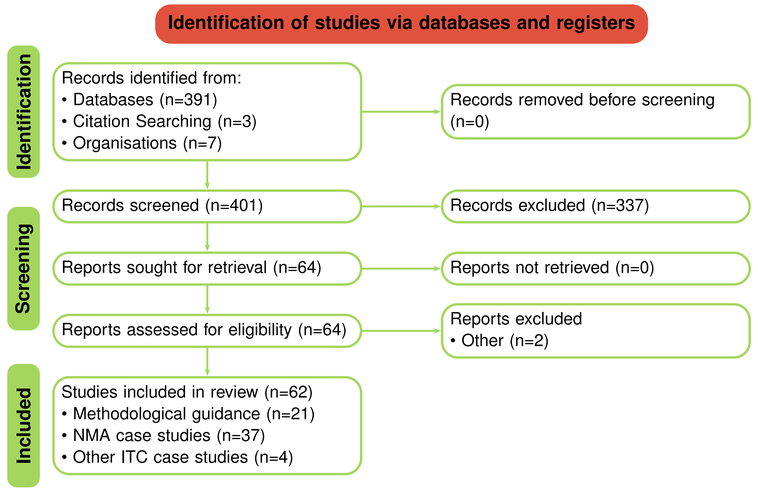

Figure 1: PRISMA flowchart depicting the identification, screening, and inclusion of 62 total publications.

Results

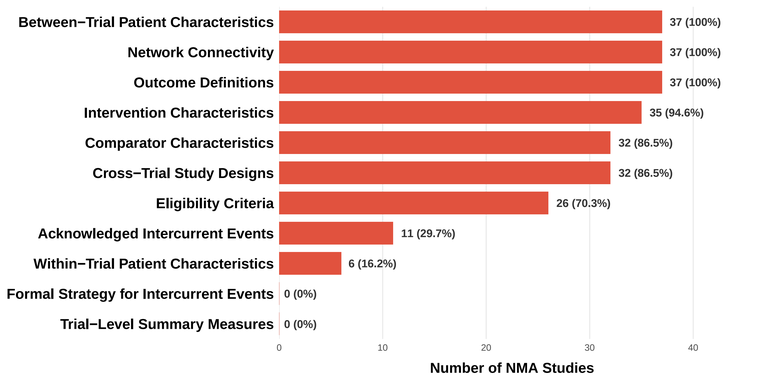

Figure 2: Compliance with traditional vs. estimand-driven feasibility reporting criteria (n=37).

- Traditional feasibility reporting is nearly 100% on connectivity, between-trial patient characteristic, and outcome definition checks, yet a critical gap exists for estimand-driven metrics, with only 29.7% of studies acknowledging ICEs and 16.2% evaluating within-trial characteristics.
- Current NMAs may be prone to structural bias as indicated by the 0% reporting of the ICE strategies and summary measures.

Discussions and Recommendations

- Confirmatory trials, especially those sponsored by the industry, are increasingly using the estimand framework lingo for reporting their results.
- Methodological guidance documents published after the ICH E9(R1) addendum call for formal integration of the estimand framework into evidence synthesis. This includes the recent methods guidance published by CDA-AMC.
- Evaluation of the current feasibility assessment practices has not started to integrate the estimand framework into NMAs.
- To incorporate the estimand framework during a feasibility assessment, our recommendations include the following:

✓ Before evaluating any data, researchers must explicitly define the target meta-analytical estimand for the entire network.

✓ Researchers must meticulously scrutinize individual trials to ensure their summary measures conceptually align with the network target, paying critical attention to exactly how intercurrent events were handled.

✓ To justify structural network connectivity, rigorous traditional checks remain mandatory. Researchers must map both within-trial and cross-trial clinical and methodological heterogeneity, focusing specifically on patient characteristics, dosing schedules, fluctuating placebo responses, and precise outcome definitions.

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