Network Meta-analyses of Real-world Evidence: A Systematic Review of Methods

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Introduction and Objective

- Network meta-analysis (NMA) compares multiple health technologies when there is a lack of head-to-head randomized controlled trials (RCT).
- NMAs generally include the results from RCTs, considered to be the gold standard of evaluation of health technologies. These NMAs can be supplemented with real-world evidence (RWE) that is lower in the hierarchy of strength of evidence.
- Study populations of RCTs are not generalizable to the target population owing to the stringent trial eligibility criteria. Real-world samples are subject to selection bias and confounding but provide evidence that reflect outcomes experienced by patients in routine clinical practice.
- NMAs using only RWE are being used in some therapeutic areas in recent years and involve analyses that are adjusted or evaluated adequately for confounders. It is valuable to understand the characteristics of such published NMAs.
- This systematic literature review (SLR) aimed to assess the quality of published RWE-only NMAs and evaluate the statistical methods used to evaluate efficacy and safety outcomes as well as account for clinical and statistical heterogeneity.

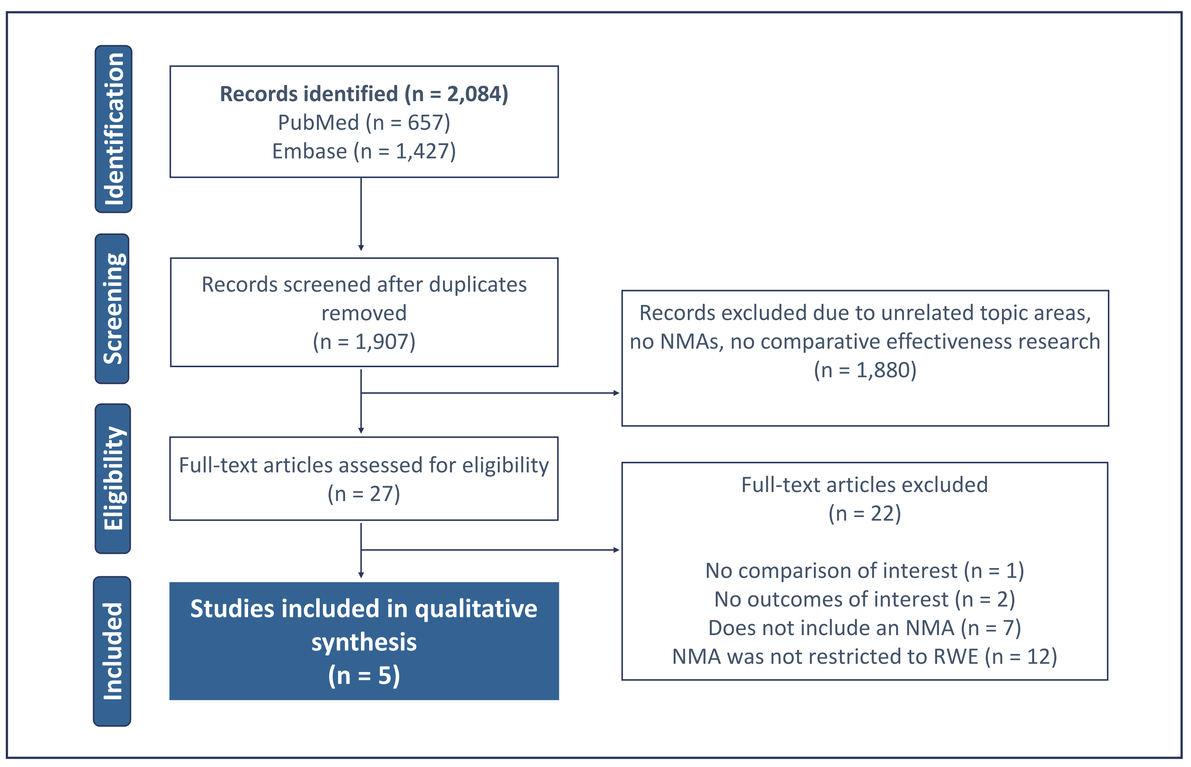
Methods

- Comprehensive searches were conducted on PubMed and Embase to identify RWE-only NMAs from the inception of the database through December 2019.
- Eligible studies could involve evaluation of any type of health intervention (pharmaceutical, procedure, policy) in any therapeutic area.
- A de-duplicated list of records from electronic databases were screened by two independent researchers: (1) title/abstract screening and (2) full-text screening.
- Conflicts in screening results were resolved by mutual discussion.
- Study characteristics and NMA methodology were extracted for eligible studies.
- Quality of included NMAs were assessed with a checklist based on International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good research practices for NMAs.[1,2,8]
- The total number of included studies were too small to conduct quantitative analysis on study metrics; descriptive statistics were reported.

Results

- Searches yielded 1,907 citations that were screened at two levels and five studies were included in this SLR. The SLR study attrition flow is shown in **Figure 1.**

Figure 1. PRISMA flow diagram



- All NMAs were conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which provides reporting standards for presentation of results.
- All included NMAs were published in the last two years.
- Four of the NMAs had no geographical limits, while one NMA was specifically in Asian patients. Other study characteristics are described in **Table 1**.
- Limited variation in treatments was observed – NMAs assessed oral anticoagulants in non-valvular atrial fibrillation and two other studies assessed surgical interventions such as liver transplantation and pancreaticoduodenectomy.
- The industry-sponsored NMA had the lowest number of included studies, but it did use a validated tool to assess study quality like other included studies.

Table 1. Characteristics of Included NMAs

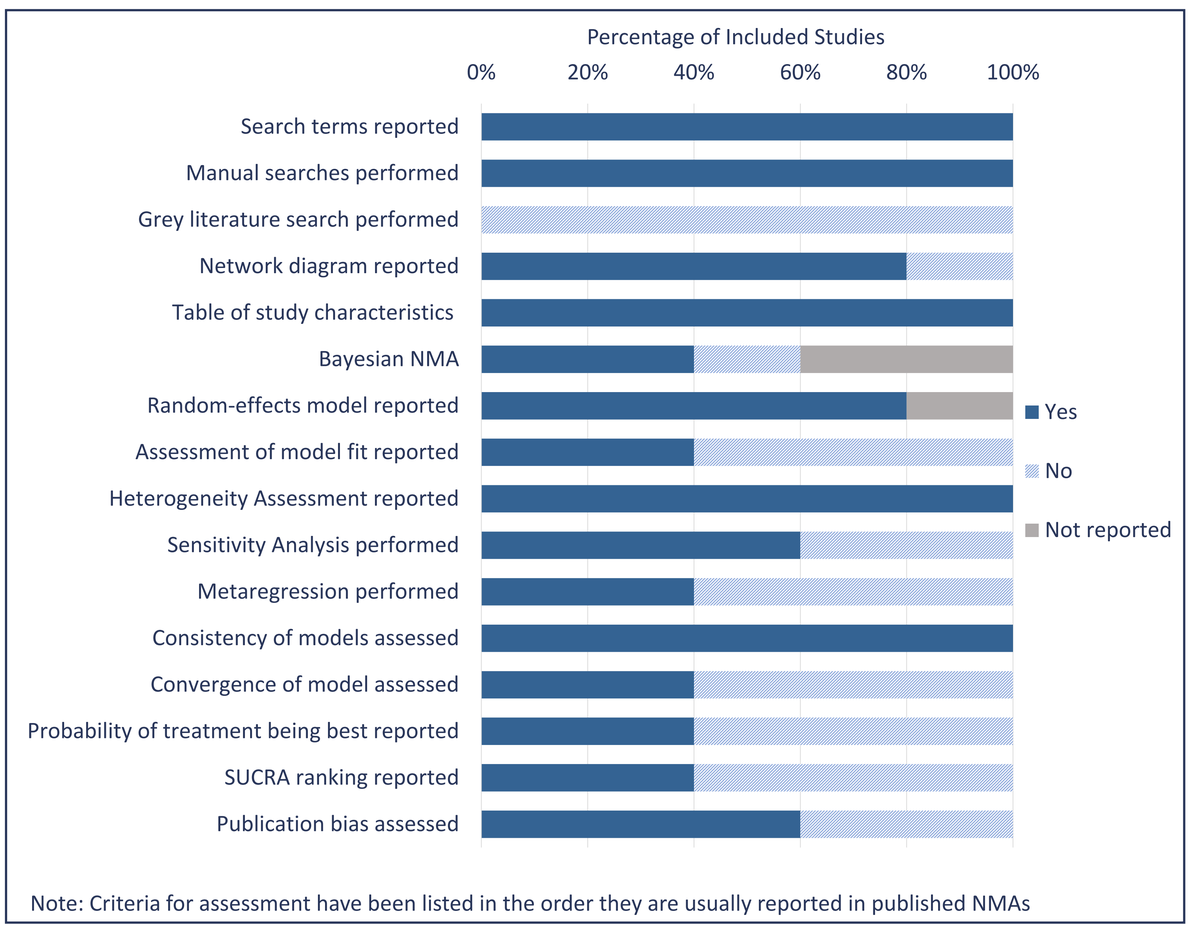
Author, Year	Journal Impact Factor	Therapeutic Area	Study Funding	Type of Study Quality Assessment	Number of Treatments Compared (Type)	Number of Included Studies	Number of Included Patients
Deitelzweig, 2018[3]	2.345	Cardiovascular/ Hematological	Industry	AHRQ	4 (Pharmaceutical)	11	NR
Gavriilidis, 2018[4]	3.526	Hepatological	Academic	NOS	3 (Surgical)	26	13,374
Hirschl, 2018[5]	1.534	Cardiovascular/ Hematological	Academic	GRADE	4 (Pharmaceutical)	88	3,351,628
Ricci, 2018[6]	2.768	Gastrointestinal	Academic	MINORS	5 (Surgical)	20	2,759
Zhang, 2018[7]	1.947	Cardiovascular/ Hematological	Grant	NOS	4 (Pharmaceutical)	16	312,827

Abbreviations: AHRQ - Agency for Healthcare Research and Quality; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; MINORS - Methodological Index for Non-randomized Studies

Results

- **Figure 2** enumerates the details of the methods used by the included studies.
- More than half the included studies that reported random-effects model estimates created NMAs using fixed-effects models as well, though these results were not reported.
- Heterogeneity was most often reported using an I^2 statistic or tau from the random-effects model, and four out the five studies performed either sensitivity or meta-regression analyses to explore potential sources of heterogeneity.
- Patient and study characteristics including study quality, publication year, geographic region, etc. were covariates used for adjustment for heterogeneity.
  - Analyses for adjustment of confounders / sources of bias were inconsistently performed and reported.
  - Risk of bias assessments varied across the studies with different tools that assess some common biases in RWE: selection, allocation, misclassification, detection, attrition, and confounding.
- Only one study used the frequentist approach reporting effect estimates with confidence intervals which cannot be interpreted as probabilities, but the study still reported SUCRA values.

Figure 2. Assessment of NMA Methods



Note: Criteria for assessment have been listed in the order they are usually reported in published NMAs

Discussion

- This SLR aimed to comprehensively identify all NMAs using only RWE and identified a limited number of studies, all of which were recently published.
- RWE-only NMAs are at risk of high overall heterogeneity, which can be partially mitigated by only including propensity-matched cohorts or performing advanced multivariable-adjusted pooled analyses.
  - There is a need to mitigate clinical and statistical heterogeneity and estimate the magnitude of effect modification due to confounders.
  - Post-hoc sensitivity analyses conducted in these NMAs helped adjust for confounding variables that could not be accounted at selection of cohorts.
  - While most NMAs identified in this SLR seem to implement them, they are not always well-reported.
- Other SLRs that evaluated published NMAs of RCTs as well as RWE found significant variation in reporting quality and statistical approaches.[8,9]
- Additional caution is warranted in interpreting RWE-only NMAs since there is a risk of under- or over-estimation of effect estimates due to risk of bias in RWE.

Conclusions and Implications

- NMAs based on RWE alone are a relatively new and emerging methodological approach in comparative effectiveness.
- Future RWE-only NMAs will need to explore novel statistical approaches that can pool generalizable data on patients using interventions of interest in actual clinical practice accounting for differences in populations, outcome measurements, and administration of interventions.
- These statistical adjustments are critical if RWE-only NMAs are to be used to derive conclusions regarding effectiveness of health technologies and support reimbursement discussions.

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