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ORIGINAL ARTICLE

Rapid network meta-analysis using data from Food and Drug Administration approval packages is feasible but with limitations

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Abstract

Objective: To test rapid approaches that use Drugs@FDA (a public database of approved drugs) and ClinicalTrials.gov to identify trials and to compare these two sources with bibliographic databases as an evidence base for a systematic review and network meta-analysis (NMA).

Study Design and Setting: We searched bibliographic databases, Drugs@FDA, and ClinicalTrials.gov for eligible trials on first-line glaucoma medications. We extracted data, assessed risk of bias, and examined the completeness and consistency of information provided by different sources. We fitted random-effects NMA models separately for trials identified from each source and for all unique trials from three sources.

Results: We identified 138 unique trials including 29,394 participants on 15 first-line glaucoma medications. For a given trial, information reported was sometimes inconsistent across data sources. Journal articles provided the most information needed for a systematic review; trial registrations provided the least. Compared to an NMA including all unique trials, we were able to generate reasonably precise effect estimates and similar relative rankings for available interventions using trials from Drugs@FDA alone (but not ClinicalTrials.gov).

Conclusions: A rapid NMA approach using data from Drugs@FDA is feasible but has its own limitations. Reporting of trial design and results can be improved in both the drug approval packages and on ClinicalTrials.gov.

Keywords: Network meta-analysis; Rapid systematic review; Drugs@FDA; ClinicalTrials.gov; Clinical trial; Comparative-effectiveness research

1. Introduction

A systematic review uses prespecified methods to identify, appraise, and synthesize relevant evidence to address a research question [1]. However, systematic reviews are not produced fast enough to meet decision-making needs [2–6]. It takes between 6 months and 2 years to conduct a systematic review [3,7,8], with a large proportion of time devoted to identifying all relevant studies by searching multiple data sources and screening thousands of records [1,9–15]. Some data sources for systematic reviews are publicly available, such as journal articles, conference abstracts, trial registrations, and regulatory documents; others such as clinical study reports and individual patient data are not readily available [11].

Pairwise meta-analysis, a quantitative component of a systematic review, can compare two interventions by combining the results of independent studies that assessed the two interventions [16,17]. Yet it falls short when multiple treatment options are available, and the goal is to compare all of them. For example, patients with open-angle glaucoma can choose among more than 10 types of topical medications (i.e., eye drops) as their initial

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What is new?

Key findings

- For a given trial, information reported was sometimes inconsistent across data sources. Journal articles provided the most information needed for a systematic review; trial registrations provided the least.
- Compared with an NMA including all unique trials, we were able to generate reasonably precise effect estimates and similar relative rankings for available interventions using trials from Drugs@FDA alone (but not ClincalTrials.gov alone).

What this adds to what is known?

- We compared not only the estimates of effect from NMAs but also a range of data needed for a systematic review, including characteristics of trials and risk of bias assessment, across bibliographic databases, Drugs@FDA, and ClinicalTrials.gov to inform the usefulness of different sources for NMA including rapid NMA.
- Rapid review with limited search is appealing for NMA. Our study added to the empirical evidence of the validity and challenges of using different data sources for NMA.

What is the implication and what should change now?

- NMA with trial data from FDA drug approval packages, which are readily available through Drugs@FDA, provides a quick snapshot of comparative-effectiveness of drug interventions of approved indications. This rapid approach can be used for time-sensitive decision-making.
- Reporting can be improved in both the drug approval packages and trial registrations.

treatment [18−20]. Network meta-analysis (NMA), an extension of pairwise meta-analysis, can compare multiple interventions in a single analysis, including indirectly comparing those interventions that have not been assessed in head-to-head trials [21,22]. The capability gained in NMA is not without cost. Compared with pairwise meta-analysis, NMA is a more resource-intensive undertaking, as it requires a broader search to include multiple interventions and studies [23,24].

Rapid reviews, defined as reviews that use methods to accelerate traditional systematic review production, have been introduced to provide timely information for decision-making in recent years [7,23]. Limiting literature search is among the most acceptable trade-offs in rapid reviews to increase efficiency [25]. For systematic reviews of products approved for market access by regulatory authorities, regulatory documents and trial registrations serve as valuable data sources [9,26]. The approval packages available from Drugs@FDA (www.fda.gov/drugsatfda) of the U.S. Food and Drug Administration (FDA) contain summaries of trials submitted to the FDA for marketing approval. These summaries were prepared by FDA staff. ClinicalTrials.gov intends to include registration and summary results of trials of FDA-regulated products and trials funded by the National Institutes of Health [27−30]. Although an earlier study found that for trials conducted between 2008 and 2012, the result reporting rate on ClinicalTrials.gov was only 38% (up to September 2013), the situation may have improved with changing landscape of trial registration and data-sharing requirements from the funders and regulators [31].

Rapid review with search limited to FDA approval packages or ClinicalTrials.gov is appealing for NMA; however, the limited search may pose a threat to the validity of findings [7,25,32]. When Trinquart et al. [33] examined the impact of reporting bias on NMA through 74 trials identified from FDA approval packages and their 51 matching journal article publications, they found that when trial results were partially or inaccurately reported in publications, the effect estimates would be biased and the relative rankings of drugs would change [33]. When Cameron et al. [34] conducted an NMA on antithrombotic medications for atrial fibrillation, they found that although only 6 of 12 published trials were registered on ClinicalTrials.gov, data from ClinicalTrials.gov alone provided similar results as those data extracted from all published trials with a fraction of time and resources. Neither study compared data from both approval packages and ClinicalTrials.gov with data from journal articles identified from bibliographic databases.

Our objective is to test rapid NMA approaches using Drugs@FDA and ClinicalTrials.gov to identify trials of drug interventions and to compare the usefulness of these two data sources with that of bibliographic databases for NMA.

2. Methods

We built on a recently published NMA conducted by our group on first-line medications for open-angle glaucoma [20]. Different from the published NMA, which focused on the comparative effectiveness of medications, this methods study aimed to inform rapid NMA.

2.1. Eligibility criteria

We used the same eligibility criteria as the previous NMA [20]. Trials were eligible if they met all of the

following criteria: (1) randomized controlled trials with parallel design; (2) 60% or more participants with primary open-angle glaucoma or ocular hypertension; and (3) compared one first-line topical glaucoma medication with another or with no treatment/placebo [20]. Trials were excluded if they (1) enrolled fewer than 10 participants in each group; (2) evaluated combination medications; or (3) followed up participants for less than 28 days after randomization [20]. The primary outcome of interest was mean intraocular pressure (IOP) at 3 months in millimeters of mercury (mmHg), the outcome on which glaucoma medications were approved by the FDA. When the 3-month IOP measure was not available, we used the IOP measured at the follow-up time closest to 3 months.

2.2. Search, data extraction, and the risk of bias assessment

The published NMA identified trials from searching bibliographic databases (searched in March 2014), including the Cochrane Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, and Embase, and Drugs@FDA (searched in April 2014).

We updated the search of Drugs@FDA in June 2018. For drugs approved before 1997, the approval packages were not available on Drugs@FDA. We, therefore, filed a request to FDA; we received no response as of July 2018. We searched ClinicalTrials.gov in December 2016. The search strategy appears in Appendix A. We discussed the limitations and implications of different search dates for the three data sources.

Two individuals independently selected the eligible trials and extracted data. Discrepancies were resolved through discussion with a third person. We used the Cochrane Risk of Bias Tool to assess the risk of bias of included trials [1].

2.3. Mapping trial reports identified from different data sources

As a trial may be reported in more than one data source (e.g., reported by a journal article and registered on ClinicalTrials.gov; reported by a journal article and described in an approval package), we used as many characteristics as possible to map different trial reports for a same trial, for example, by the trial registration number and the trial publication link provided by ClinicalTrials.gov, the sponsor of the trial, the intervention and comparator, and number of participants randomized.

2.4. Qualitative and quantitative synthesis

When a trial was identified from more than one source, we compared the reporting of key characteristics, including population, intervention, comparison, and primary and secondary outcomes (PICO), statistical methods, baseline characteristics, and results. We examined the completeness and consistency of information provided in different data sources.

For quantitative synthesis, we analyzed five networks of trials: (1) all unique trials identified from three data sources (i.e., bibliographic databases, Drugs@FDA, and ClinicalTrials.gov), hereby referred to as "all unique trials"; (2) trials identified from bibliographic databases alone, hereby referred to as "published trials"; (3) trials identified from Drugs@FDA alone, hereby referred to as "FDA trials"; (4) trials identified from ClinicalTrials.gov alone, hereby referred to as "Clinical trials"; and (5) trials identified from bibliographic databases but not found on Drugs@FDA or ClinicalTrials.gov, hereby referred to as "published trials without overlaps." For all unique trials, when data for one trial were available from more than one source, we used data from the sources following this order of priority: Drugs@FDA, bibliographic databases, and ClinicalTrials.gov.

For each network, we first conducted pairwise meta-analyses for every direct comparison using a DerSimonian and Laird random-effects model [35], implemented using Stata package "metan" [36−38]. We then fit random-effects NMA models following the multivariate approach by Chaimani and White, executed using packages "mvmeta," "network," and "network graphs" assuming a common heterogeneity across all comparisons in the network [38−40]. We generated the relative effect estimates (mean difference in IOP) between any two interventions in the network and used the mean rank to compare interventions.

To evaluate the consistency of results from the three different data sources, we derived a test statistic based on a discrepancy measure of the effect estimates from each data source. The test statistic follows a chi-square distribution under the null hypothesis where two data sources are consistent having all the same true effect sizes. A detailed description of the test statistic is provided in Appendix B.

2.5. Evaluating NMA assumptions and sensitivity analyses

The indirect comparisons made in NMA are built on the assumptions of transitivity and consistency [41]. The transitivity assumption indicates that the indirect comparison is a valid estimation of the unobserved direction comparison, the validity of which can be conceptually evaluated [41]. The transitivity assumption is likely to hold in our data because the interventions analyzed are all first-line medications for the same condition [41,42]. The consistency assumption implies agreement between direct and indirect estimates, which can be tested statistically [41]. We evaluated the consistency assumption using three approaches: loop-specific approach, modeling inconsistency approach, and side-split approach [40,43−47]. When statistical inconsistency was detected, we first examined the trial characteristics and then conducted sensitivity analysis by removing trials that were suspected to have introduced statistical inconsistency [42]. For trials missing precision

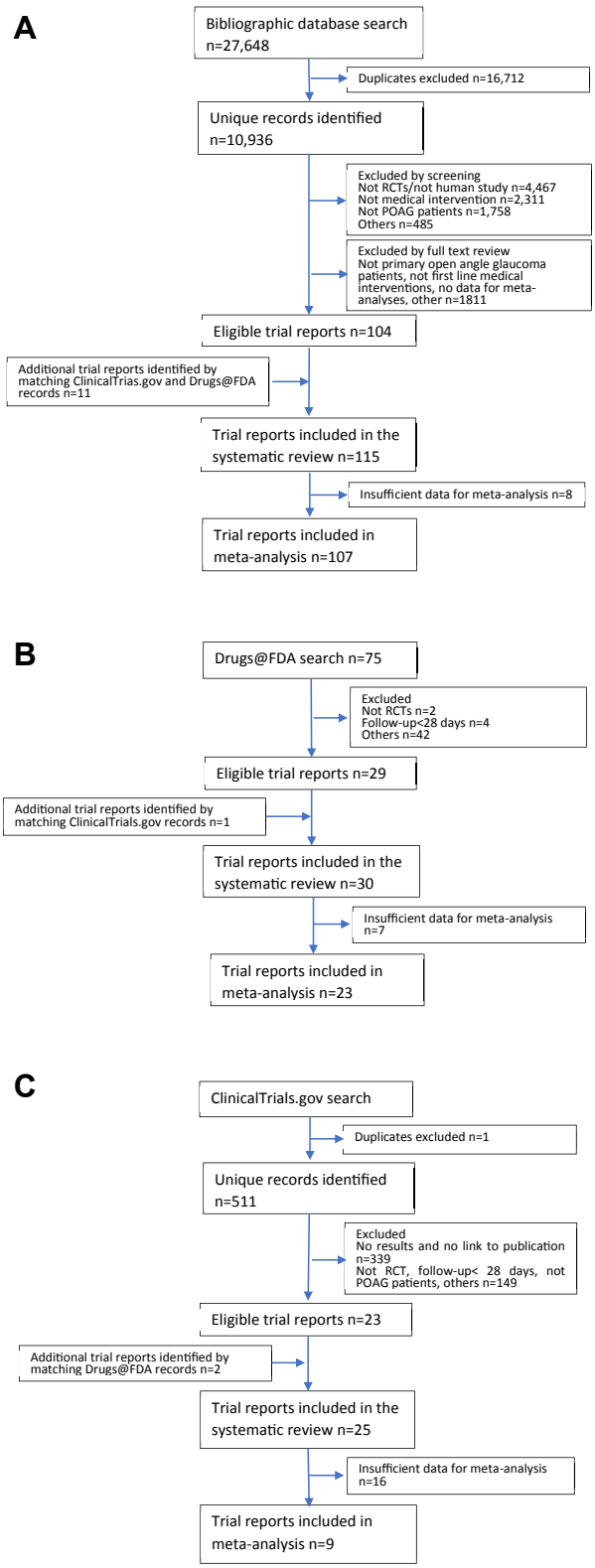

Fig. 1. Identification of trials. (A) Identification of trials from bibliographic databases. (B) Identification of trials from Drugs@FDA. (C) Identification of trials from ClinicalTrials.gov. *Abbreviations*: RCT, randomized controlled trials. POAG, primary open angle glaucoma.

measures (e.g., standard deviations [SDs]), we imputed the SDs by calculating the weighted averages of SDs from other studies of the same comparison and included them in the NMAs as a sensitivity analysis.

We used STATA 14 (StataCorp LP, College Station, TX) for all analyses.

3. Results

3.1. Identification of trials

We identified 115 journal articles from bibliographic databases, 30 approval packages from Drugs@FDA, and 25 trial registration entries from ClinicalTrials.gov (Fig. 1). These records described 138 unique trials including 29,394 participants. Trials from Drugs@FDA and ClinicalTrials.gov each contributed about one-third of all participants (12,624 and 9,817, respectively). The extent of overlap of trials among the three data sources is shown in Fig. 2 with individual trial reports listed in Appendix C and D. Ninety one percent (125/138) trials provided sufficient data (effect estimates and

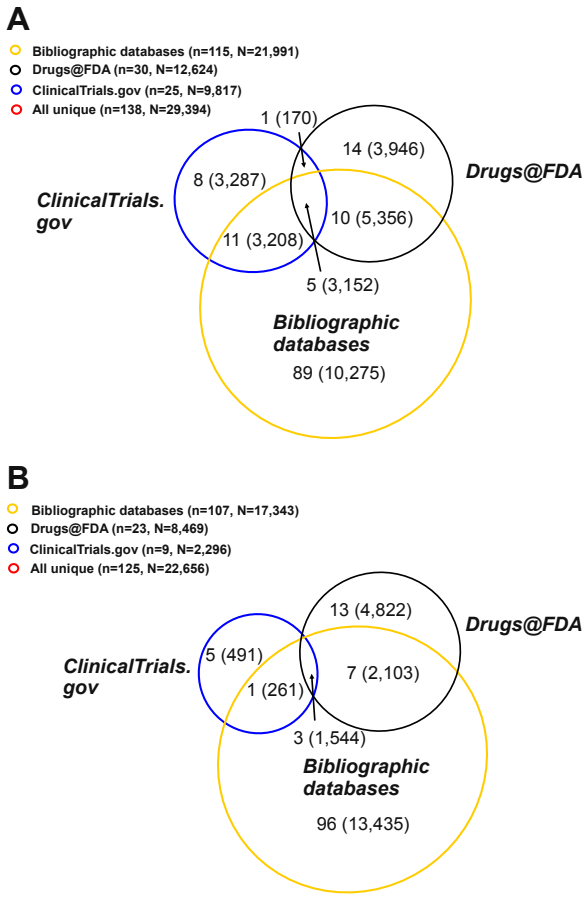

Fig. 2. The extent of overlap of trials among bibliographic database, Drugs@FDA, and ClinicalTrials.gov. (A) All included trials. (B) Trials with sufficient data for meta-analysis. *Abbreviations*: *n*, number of trials; *N*, total number of participants.

precision measures) for pairwise meta-analysis and NMA of IOP at 3 months (Fig. 2).

3.2. Characteristics of included trials

The characteristics of included trials by data source are described in Appendix E. For trials identified from bibliographic databases, Drugs@FDA, and ClinicalTrials.gov, the years of trial completion range from 1983 to 2016, 1997 to 2012, and 1993 to 2014, respectively; the median sample sizes were 111, 350, and 267, respectively. Most trials were multicenter trials. The median follow-up time was 3 months. Because of the relatively narrow eligibility of the underlying NMA, the interventions compared and participants enrolled across trials were comparable, unlikely violating the transitivity assumption.

3.3. Risk of bias assessment

Assessing the risk of bias was challenging for trials identified from Drugs@FDA and ClinicalTrials.gov because details about trial design and conduct were generally not available in these two sources. For example, most approval packages and trial registration entries did not describe random sequence generation and allocation concealment (unclear risk of bias): 93% for Drugs@FDA and 100% for ClinicalTrials.gov.

Reporting for masking was inadequate across all three sources. Many trials (>70%) reported single, double, or triple masking but did not specify the role of a person who was masked. Also, most trials were funded by the pharmaceutical industry: 60%, 100%, and 92% for trials identified from bibliographic databases, Drugs@FDA, and ClincalTrials.gov, respectively. Risk of bias assessments for individual trials and a figure illustration is available in Appendix F and G.

3.4. Comparison of reporting of key characteristics of trials

For trials identified from more than one data source, a comparison of the reporting of key characteristics is available in Appendix H. Journal articles and FDA approval packages generally provided more trial information than ClinialTrials.gov registrations did. Such information includes descriptions of patient characteristics, interventions (drug dose and regimen), statistical methods (sample size calculation, type of analysis, and methods of handling missing data), and results. Of note, 32% (8/25) of trials from ClinicalTrials.gov have no results posted. FDA approval packages provided more information about secondary outcomes and adverse events of trials than the other two sources. Eligibility criteria, primary outcome, and primary analysis sometimes disagreed across sources. The quantitative results of IOP at 3 months generally agreed. We summarize the strengths and limitations of each data source for systematic review in Table 1.

3.5. Comparison of quantitative results

We included trials with sufficient data in meta-analyses and NMAs (Fig. 2). Summary information for each network of trials is available in Appendix I. The number of interventions analyzed differed across networks: 15 for all unique trials with 39 direct comparisons, 14 for published trials with 36 direct comparisons, 12 for FDA trials with 16 direct comparisons, 6 for ClinicalTrials.gov trials with 5 direct comparisons, and 14 for published trials without overlaps with 16 direct comparisons.

3.5.1. Pairwise meta-analyses

The estimates of the mean difference in IOP at 3 months derived from pairwise meta-analyses of different networks of trials are available in Appendix J. The effect estimates generally agree across different networks, although precisions varied. In addition, substantial heterogeneity ($I^2 > 50\%$) in results was found for some drug comparisons in published trials and ClinicalTrials.gov trials but not in FDA trials.

3.5.2. NMAs

The structure of different networks of trials is displayed in Fig. 3. The networks of all unique trials, published trials, and published trials without overlaps are well-connected polygons; the network of FDA trials is star shaped where interventions were mostly compared with a common comparator but not with one another; the network of ClinicalTrials.gov trials is poorly connected (Fig. 3).

The mean ranks for each drug and placebo derived from the network of all unique trials are presented in Table 2. The effect estimates, ranking probabilities, and mean ranks are all consistent with one another.

The results of NMAs derived from other networks of trials (published trials, FDA trials, ClinicalTrials.gov trials, and published trials without overlaps) are available in Appendix K-L.

The effect estimates are shown in Fig. 4. The direction and size of effect generally agreed across different data sources although precisions varied. Of note, for bimatoprost and travoprost, where NMAs of published trials and FDA trials found statistically significant differences in IOP reduction compared with timolol, the NMA of ClinicalTrials.gov trials failed to detect statistically significant differences.

A global test for the null hypothesis that two data sources are consistent with the same true effect sizes across all comparisons found a statistically significant *P*-value between the effect estimates from FDA trials and published trials, but the differences in the size of the effect estimates are small and clinically unimportant. Owing to the limited number of nonoverlapping trials identified from

Table 1. Strengths and limitations of each data source for systematic review and network meta-analysis

Sources	Strengths	Limitations
PICO (patient, intervention, comparison, and outcome) and study design		
Bibliographic database	• Index a large number of trials • Provide detailed descriptions for interventions (e.g., dose, schedule) • Provide most information about the trial design, statistical methods, and details for assessing risk of bias	• Provide limited information about secondary outcomes and adverse events
Drugs@FDA	• Provide information about secondary outcomes and adverse events that may not be available elsewhere • Useful for identifying unpublished trials of regulated products • Usually contain more information about missing data (and how they were handled); sometimes useful for assessing risk of bias	• Only useful for products regulated by FDA • Approval packages before 1997 not readily available online • Description of administration of interventions may be incomplete • Provide limited information about the trial design
ClinicalTrials.gov	• Useful for identifying unpublished trials of all types of interventions (including interventions not regulated by FDA) • Provide PICO in a tabulated format	• Not all trials (and interventions evaluated in those trials) before 2000 are available • Registration may be incomplete; not all results are available • Provide limited information about secondary outcomes and adverse events of trials • Provide very limited information about the trial design and statistical methods; not useful for assessing risk of bias
Reporting of results		
Bibliographic databases	• Almost always provide information about baseline characteristics • Provide reasonably complete information about result and precision measures	• Patient flow diagram not always available
Drugs@FDA	• Provided results at all time points	• Provided limited information about baseline characteristics and patient flow • Precision measures may not be reported
ClinicalTrials.gov	• Provide detailed information about patient flow	• Provide limited information about baseline characteristics • Results may not be posted
Time and resources needed for trial identification and data extraction		
Bibliographic databases	• Substantial amount of time and resources needed for trial identification and data extraction	
Drugs@FDA	• Efficient for trial identification • Some obstacles for data extraction because of unstructured format for results reporting	
ClinicalTrials.gov	• Efficient for trial identification • Most efficient for data extraction because results are reported in a structured format	

ClinicalTrials.gov, we failed to find evidence for the inconsistency of estimates between FDA trials and ClinicalTrials.gov trials or between published trials and ClinicalTrials.gov. Detailed results of the evaluation of the consistency of evidence between data sources are available in Appendix M.

Table 2 presents the mean ranks generated by NMAs of different networks of trials. Across different networks, the relative rankings were stable for drugs (drug A always better than drug B) that are among the highest and lowest ranks, but not for drugs among the middle ranks. Note that relative rankings should not be overinterpreted as small differences in effect estimates may not be clinically important.

3.5.3. Evaluation of inconsistency and sensitivity analyses (Appendix N and O)

We detected evidence of statistical inconsistency in networks of all unique trials, published trials, and published trials without overlaps. However, inconsistency models did not improve the model fit. Inconsistency assessment did not apply to ClinicalTrials.gov trials because there was no closed loop in the network, that is, no direct vs. indirect evidence. Inconsistency assessment was also not

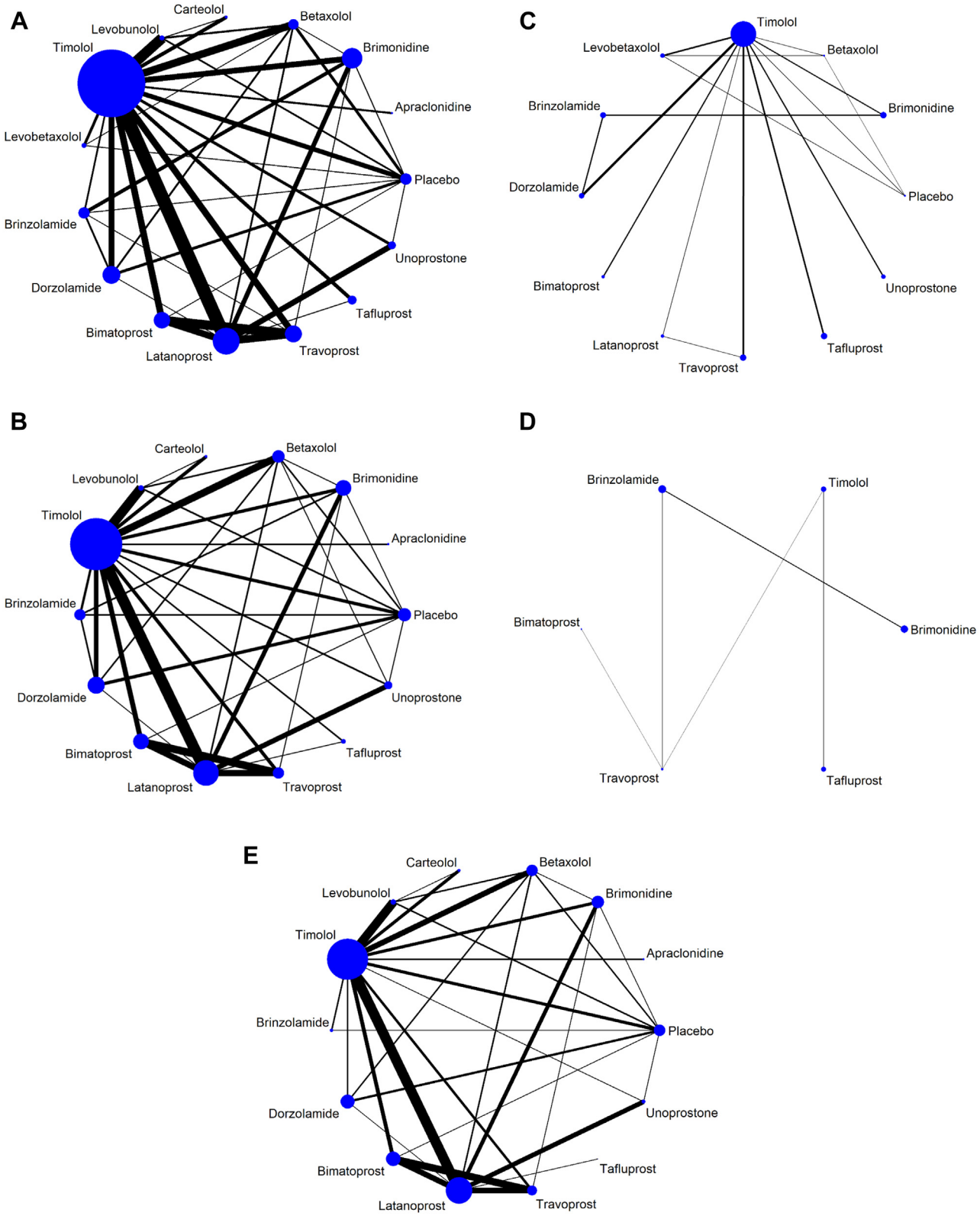

Fig. 3. Network graphs. (A) All unique trials. (B) Published trials. (C) FDA trials. (D) ClinicalTrials.gov trials. (E) Published trials without overlaps. Across graphs, the node size is scaled by the percentage of total participants in a network, and the edge width is scaled by the percentage of total trials in a network. Within a graph, the node size is proportional to the number of participants randomized to the medication, and the line thickness is proportional to the number of trials directly comparing the connected two medications.

Table 2. The mean ranks generated by network meta-analyses

	Mean rank				
	Trials				
Drugs	All unique	Published	Drugs@FDA	Clinical Trials.gov	Published without overlap
Bimatoprost	1	1.1	1	2	1.6
Travoprost	2.4	3.2	2.4	1.7[a]	3.4
Latanoprost	3.3	3.5	2.6	/	3.6
Levobunolol	3.6	4	/	/	4.2
Tafluprost	5.3	3.3[a]	4.9	2.9	2.6[a]
Timolol	6.1	6.3	4.1[a]	4	6.3
Carteolol	7	7.1	/	/	7.3
Brinzolamide	8.1	9.9	6.5	4.5	9.6
Brimonidine	10	8.1[a]	10.5[a]	5.8	8[a]
Levobetaxolol	10.3	/	7.3	/	/
Dorzolamide	11.2	10.5	7.8	/	10.8
Betaxolol	11.7	10.4[a]	9.8	/	10.5[a]
Apraclonidine	11.9	11.4	/	/	11.2
Unoprostone	13.1	12.2	9.3[a]	/	11.9
Placebo	15	14	11.7	/	14

Abbreviations: FDA, U.S. Food and Drug Administration; NMA, network meta-analysis.
[a] Indicates that the rank of a certain drug derived from NMA of a trial network differs from that derived from NMA of all unique trials.

applicable to FDA trials because although there were closed loops in the network, they are from multi-arm trials, that is, no direct vs. indirect evidence. The results from the sensitivity analyses (addressing statistical inconsistency and missing SDs) were consistent with our primary analyses.

4. Discussion

In this study, we tested the feasibility of rapid approaches for NMA by restricting searches to different data sources. We found that compared with a comprehensive approach of searching all data sources, for drugs regulated by FDA, searching FDA approval packages alone can identify 22% of all trials, which covered 80% of interventions (43% of participants). Identifying trials and collecting data from the FDA approval packages were straightforward and time-saving. NMA of these trials provided reasonably precise effect estimates and relatively consistent rankings. Also, FDA approval packages generally provided more trial information regarding PICO, statistical methods, and results than ClinialTrials.gov registrations did, although both of them provided insufficient information for risk of bias assessment, compared with journal articles. In contrast, rapid NMA approach of searching ClinicalTrials.gov alone was less successful and may not produce valid and reliable findings.

FDA approval packages have been used by previous studies as a ‘‘gold standard’’ to examine publication bias and reporting bias and their impacts on systematic review [33,48–50].

Our study generates new empirical evidence that FDA approval packages alone could serve as a valid data source for rapid NMAs of drug interventions for approved indications. Based on our findings, conducting a rapid NMA with trial data from FDA approval packages would be an efficient choice for decision-makers who need a quick snapshot of comparative effectiveness of drugs for approved indications. Identifying trials from Drugs@FDA requires much less time and resources than a comprehensive search. The search is straightforward as only a drug’s generic name is needed.

One caveat is that not all FDA approval packages are readily available. Approval packages are available on Drugs@FDA for drugs approved since 1997 and only for approved indications [51]; for drugs approved before 1997, information must be requested through a freedom of information request (https://www.accessdata.fda.gov/scripts/foi/FOIRequest/Requestinfo.cfm). During our study, we did not receive a response to our request from the FDA. Also, the precision measures for the primary outcome of these pivotal trials were not always reported (23% missing rate in our case), limiting the usefulness of approval packages for NMA. In addition, the FDA approval packages provide limited information on design and intervention characteristics for the evaluation of transitivity assumption. Furthermore, because the comparator chosen in FDA trials is usually placebo or standard of care (timolol in our example), the network formed by these trials may not be well connected, limiting the statistical power for NMA and for examining the consistency assumption for NMA.

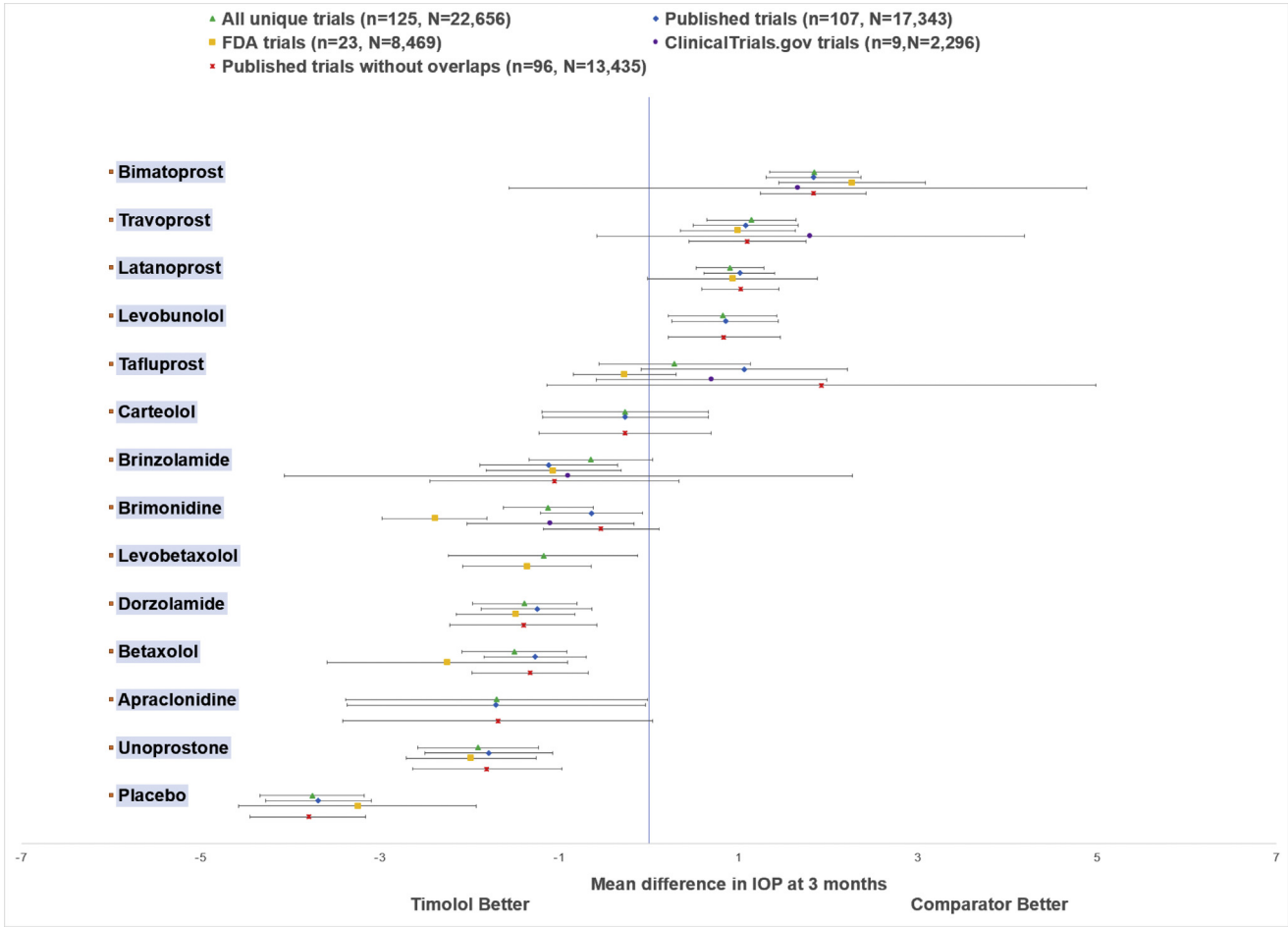

Fig. 4. Estimated mean difference in IOP at 3 months derived from network meta-analyses (relative to timolol). Medications with effect estimates (markers) and confidence intervals (lines) on the right are better than timolol in reducing IOP at 3 months. Medications with effect estimates (markers) and confidence intervals (lines) on the left are worse than timolol in reducing IOP at 3 months. *Abbreviations*: IOP, intraocular pressure.

Among three data sources, ClinicalTrials.gov provided the least complete trial information. Most trials completed before the existence of the database in 2000 were not available. Trial results collected before the launch of the result database in 2008 were not available. In addition, ClinicalTrials.gov only requires summary information about a trial protocol and results, limiting its usefulness for systematic reviews.

Ideally, all trial reports should be indexed in one place and the list should be kept up to date. Also, findings from trials should be presented in a complete and consistent way to facilitate systematic reviews. At the current time, searching one data source cannot identify all relevant trials and trial information provided by data sources is far from complete. In addition, disagreements were found across data sources in eligibility criteria, primary outcome, and primary analysis by our study and other studies [11,52–57]. With inconsistent eligibility criteria, it is difficult for health care professionals and researchers to interpret and apply the trial findings. The inconsistency in describing the primary outcomes and the primary analyses is also problematic because results could be selectively reported by trialists to better align with their hypotheses.

For regulatory agencies with an increasingly open attitude toward data sharing, our findings shed light on the scope and quality of trial information shared with the public. As proposed by some [58], FDA should consider integrating components of the CONSORT (Consolidated Standards of Reporting Trials) [59] in its description of trials. In addition to approval packages, the recent FDA pilot program of sharing clinical study reports is also a promising step forward [60]. For trial registries, our findings highlight the incompleteness of information registered. The minimal data elements required are insufficient for the purpose of systematic reviews. The requirement of trial protocol submission and results posting may mitigate this problem [60].

Our study is a case study on first-line glaucoma medications. We only examined regulatory documents from FDA and registrations from ClinicalTrials.gov. Therefore, our conclusions should not be overly generalized. A recent study by Marshall et al. [61] highlighted the potential

problems in limiting search in 2,512 Cochrane systematic reviews with pairwise meta-analysis. In addition, for research questions with only a smaller number of trials, the usefulness of any rapid approach is diminished. We recognize that we searched the three databases at different time points. However, only two of the 27 eligible trials identified from ClincialTrials.gov were completed after April 2014. Excluding these two trials is unlikely to change our key findings and conclusions.

In terms of strengths, we conducted a full range of comparisons of trial information on PICO, statistical methods, baseline characteristics, and results. Our study enriched the empirical evidence on the utility of a rapid approach for NMA. Future research should test this approach in other clinical areas, in the assessment of long-term clinical outcomes and adverse events, and in the exploration of other data sources such as clinical study reports and individual patient data.

5. Conclusions

A rapid NMA approach using data from Drugs@FDA is feasible but has its own limitations. Reporting of trial design and results can be improved in both the drug approval packages and on ClinicalTrials.gov.

CRediT authorship contribution statement

Lin Wang: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Benjamin Rouse:** Validation, Investigation, Data curation, Writing - review & editing, Visualization. **Arielle Marks-Anglin:** Methodology, Software, Formal analysis. **Rui Duan:** Methodology, Software, Formal analysis. **Qiyuan Shi:** Conceptualization, Methodology, Investigation, Data curation. **Kevin Quach:** Software, Formal analysis. **Yong Chen:** Methodology, Supervision. **Christopher Cameron:** Methodology, Supervision. **Christopher H. Schmid:** Methodology, Supervision. **Tianjing Li:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Supplementary data

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References

[1] Higgins JPT. GSe. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available at http://handbook.cochrane.org.
[2] Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007;147:224−33.
[3] Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, Moher D. Systematic reviews can be produced and published faster. J Clin Epidemiol 2008;61:531−6.
[4] Beller EM, Chen JK, Wang UL, Glasziou PP. Are systematic reviews up-to-date at the time of publication? Syst Rev 2013;2:36.
[5] Tsafnat G, Glasziou P, Choong MK, Dunn A, Galgani F, Coiera E. Systematic review automation technologies. Syst Rev 2014;3:74.
[6] Hartling L, Guise JM, Kato E, Anderson J, Aronson N, Belinson S, et al. AHRQ comparative effectiveness reviews. In: EPC methods: an exploration of methods and context for the production of rapid reviews. Rockville, MD: Agency for Healthcare Research and Quality (US); 2015.
[7] Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implement Sci 2010;5:56.
[8] Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Syst Rev 2012;1:10.
[9] AHRQ Methods for Effective Health Care. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008.
[10] Halladay CW, Trikalinos TA, Schmid IT, Schmid CH, Dahabreh IJ. Using data sources beyond PubMed has a modest impact on the results of systematic reviews of therapeutic interventions. J Clin Epidemiol 2015;68:1076−84.
[11] Mayo-Wilson E, Li T, Fusco N, Dickersin K. Practical guidance for using multiple data sources in systematic reviews and meta-analyses (with examples from the MUDS study). Res Synth Methods 2018;9:2−12.
[12] Institute of Medicine. Finding what works in health care: standards for systematic reviews. Washington, FC: The National Academies Press; 2011.
[13] Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med 2016;13:e1002028.
[14] Rosman LTC, Li M, Li T, Saldanha I, Dickersin K. Teaching searching in an intensive systematic review course: "how many citations should I expect to review?". Quebec, Canada: Cochrane Colloquium; 2013.
[15] Wallace BC, Trikalinos TA, Lau J, Brodley C, Schmid CH. Semi-automated screening of biomedical citations for systematic reviews. BMC Bioinformatics 2010;11:55.
[16] Chalmers I. The cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. Ann N Y Acad Sci 1993;703:156−63. [discussion 63-65].
[17] Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. Clin J Am Soc Nephrol 2008;3:253−60.
[18] Boland MV, Ervin AM, Friedman D, Jampel H, Hawkins B, Volenweider D, et al. AHRQ comparative effectiveness reviews. In: Treatment for glaucoma: comparative effectiveness. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.
[19] Boland MV, Ervin AM, Friedman DS, Jampel HD, Hawkins BS, Vollenweider D, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158:271−9.
[20] Li T, Lindsley K, Rouse B, Hong H, Shi Q, Friedman DS, et al. Comparative effectiveness of first-line medications for primary

open-angle glaucoma: a systematic review and network meta-analysis. Ophthalmology 2016;123:129−40.
[21] Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med 2011;9:79.
[22] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163−71.
[23] Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm Pract 2017;15:943.
[24] Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Intern Emerg Med 2017;12:103−11.
[25] Hartling L, Guise JM, Hempel S, Featherstone R, Mitchell MD, Motu'apuaka ML, et al. Fit for purpose: perspectives on rapid reviews from end-user interviews. Syst Rev 2017;6:32.
[26] Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database Syst Rev 2007Mr000010.
[27] Vandvik PO, Brignardello-Petersen R, Guyatt GH. Living cumulative network meta-analysis to reduce waste in research: a paradigmatic shift for systematic reviews? BMC Med 2016;14:59.
[28] NIH policy on the dissemination of NIH-funded clinical trial information. In: Health NIo. Bethesda, MD: National Institutes of Health; 2016:64922−8.
[29] Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA 2016;316:1353−4.
[30] Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. N Engl J Med 2016;375:1998−2004.
[31] Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. Compliance with results reporting at ClinicalTrials.gov. N Engl J Med 2015;372:1031−9.
[32] Tsertsvadze A, Chen YF, Moher D, Sutcliffe P, McCarthy N. How to conduct systematic reviews more expeditiously? Syst Rev 2015;4:160.
[33] Trinquart L, Abbe A, Ravaud P. Impact of reporting bias in network meta-analysis of antidepressant placebo-controlled trials. PLoS One 2012;7:e35219.
[34] Cameron C. Enhancing the use of network meta-analysis to synthesize information on benefits and harms of drugs to support regulatory and reimbursement decisions in Canada: School of Epidemiology. Ottawa, Canada: Public Health and Preventive Medicine University of Ottawa; 2015.
[35] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177−88.
[36] Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. Metan: fixed- and random-effects meta-analysis. Stata J 2008;8:3−28.
[37] White IR. Multivariate random-effects meta-regression: updates to mvmeta. Stata J 2011;11:255−70.
[38] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.
[39] Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. Stata J 2015;15:905−50.
[40] White IR. Network meta-analysis. Stata J 2015;15(4):951−85.
[41] Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80−97.
[42] Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med 2013;11:159.
[43] Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002;21:2313−24.
[44] Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932−44.
[45] Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98−110.
[46] White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012;3:111−25.
[47] Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33:641−56.
[48] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252−60.
[49] Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. BMJ 2012;344:d7202.
[50] Roest AM, de Jonge P, Williams CD, de Vries YA, Schoevers RA, Turner EH. Reporting bias in clinical trials investigating the efficacy of second-generation antidepressants in the treatment of anxiety disorders: a report of 2 meta-analyses. JAMA Psychiatry 2015;72:500−10.
[51] Turner EH. How to access and process FDA drug approval packages for use in research. BMJ 2013;347:f5992.
[52] Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA 2009;302:977−84.
[53] Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR. Comparison of protocols and registry entries to published reports for randomised controlled trials. Cochrane Database Syst Rev 2011Mr000031.
[54] Scherer RW, Huynh L, Ervin AM, Taylor J, Dickersin K. ClinicalTrials.gov registration can supplement information in abstracts for systematic reviews: a comparison study. BMC Med Res Methodol 2013;13:79.
[55] Becker JE, Krumholz HM, Ben-Josef G, Ross JS. Reporting of results in ClinicalTrials.gov and high-impact journals. JAMA 2014;311:1063−5.
[56] Hartung DM, Zarin DA, Guise JM, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med 2014;160:477−83.
[57] Halfpenny NJ, Quigley JM, Thompson JC, Scott DA. Value and usability of unpublished data sources for systematic reviews and network meta-analyses. Evid Based Med 2016;21:208−13.
[58] Bennett DA, Jull A. FDA: untapped source of unpublished trials. Lancet 2003;361:1402−3.
[59] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
[60] Li T. What's not shared—building on the FDA's transparency momentum. BMJ 2018. Available at https://blogs.bmj.com/bmj/2018/01/31/tianjing-li-whats-not-shared-building-on-the-transparency-momentum/.
[61] Marshall IJ, Marshall R, Wallace BC, Brassey J, Thomas J. Rapid reviews may produce different results to systematic reviews: a meta-epidemiological study. J Clin Epidemiol 2019;109:30−41.