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The systematic review and bibliometric network analysis (SeBriNA) is a new method to contextualize evidence. Part 1: description

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Abstract

Objective: We describe a new methodology, the systematic review and bibliometric network analysis (SeBriNA), to contextualize the quality and quantity of patient-centered outcomes evidence relative to complementary documents such as reviews, practice guidelines, editorials, and media reports.

Study Design and Setting: The SeBriNA is informed by systematic review and bibliometric analysis methodologies. It focuses on two key concepts: 1) quality of evidence for patient-centered outcomes using cumulative meta-analysis and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) appraisal approach; 2) quantity of original research and its citation relationships to related documents. It includes four steps: 1) research questions and document selection; 2) data extraction and analysis; 3) document network relationships; and 4) document network visualization.

Results: The primary output from the SeBriNA is an analysis of 1) evidence—the annual cumulative meta-analysis estimate of effect juxtaposed against quality of evidence by patient-centered outcomes (GRADE), and 2) context—the network of relationships between related documents and original research. This analysis can be represented as a single figure.

Conclusions: The SeBriNA may help decision makers conceptualize, interpret, and visualize the quantity, quality, and relevance of original research within a network of related documents. Applications include prospective support for clinical and policy decisions and identification of research gaps.

Keywords: Evidence-based medicine; Bibliometrics; Systematic reviews; Cumulative meta-analysis; Publication bias; Patient-centered outcomes

1. Introduction

The optimal time to introduce new health care technologies into routine care is controversial. Data from pragmatic, well-designed, and well-executed randomized controlled trials (RCTs) are typically viewed as the most rigourous form of scientific evidence available to inform new health care technology decisions. However, waiting for fully published RCTs may not always be possible or appropriate. Further, factors other than scientific evidence may influence demands for promising new health care technologies [1].

Documents such as media reports, editorials, or practice guidelines may have tremendous influence in knowledge uptake [2], and may vary widely from selective to comprehensive in their use of scientific evidence to support their claims. For example, media reports in the United Kingdom focused on a small case series of 12 children highlighting a potential association between the measles, mumps, and rubella vaccination and autism. A striking temporal relationship was subsequently seen with a decrease in pediatric vaccination rates and an increase in measles cases despite the high risk of study bias inherent in case series [3] and despite six large population-based studies consistently suggesting no relationship [4]. Although the case series report was ultimately retracted [3,5,6], the negative global public health consequences continue.

With an increasing evidence imperative and demands for transparency in the methodology underpinning clinical

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What is new?

Key finding

- We describe a new methodology, the systematic review and bibliometric network analysis (SeBriNA), to contextualize the quality and quantity of patient-centered outcomes evidence relative to complementary documents such as reviews, practice guidelines, editorials, and media reports.

What this adds to what was known?

- The SeBriNA focuses on two key concepts: 1) quality of evidence for patient-centered outcomes using cumulative meta-analysis and the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) appraisal approach, and 2) quantity of original research and its citation relationships to related documents.
- The primary output from the systematic bibliometric review is an analysis of 1) the evidence—the annual cumulative meta-analysis estimate of effect juxtaposed against quality of evidence by patient-centered outcomes (GRADE), and 2) the context—the network of relationships between related documents and original research.

What is the implication, what should change now?

- Potential applications of this methodology include prospective support for clinical and policy decisions, particularly in situations of uncertainty, and identification of research gaps.

recommendations, we need a methodology to organize, synthesize, and interpret the context of original research evidence in other forms of evidence and knowledge. Systematic reviews address a specific clinical question using specific methodologies to minimize bias and improve the precision of estimates (i.e., reduce random error [7]); however, their interpretation is limited to the original research study data included in the review and do not contextualize the evidence within other document types. For example, a systematic review can only make inferences based on a synthesis of the original research identified by the search strategy, and could not address the quality of the evidence underpinning media reports of the public's perceived perception of the effectiveness of a new drug. Although systematic reviews and media reports may both cite original research evidence, the actual cited evidence may differ, and we currently do not have a methodology to explicitly identify and compare the types of cited evidence for further discussion.

Bibliometrics is a methodology from library science that is defined as, "the application of mathematics and statistical methods to books and other media of communication" [8,9]. By studying communication media, bibliometric analyses can "illuminate the processes of science and technology by means of counting documents" [9]. Examples of bibliometric analyses include determination of the research use of books and journals by an institution and the impact factor. However, bibliometric analyses do not synthesize data, assess study quality, or interpret findings of original research data. Individually, systematic reviews and bibliometric studies provide important insights to study a new health care technology; however, we still have a gap in the methodological literature to simultaneously summarize *and* contextualize the evidence base of a new health care technology. Herein, we propose a new methodology combining the strengths of systematic reviews and bibliometrics to achieve this goal, the *s*ystematic r*e*view and *b*ibliomet*ric* *n*etwork *a*nalysis (SeBriNA).

In this article, we describe the new SeBriNA methodology as a refined way of understanding: 1) the quantity and quality of original research in a new health care technology and 2) how original research was represented by related documents, such as review articles, practice guidelines, editorials, letters to the editor, and media reports. The SeBriNA includes four key steps: 1) research questions and document selection; 2) data extraction and analysis; 3) document network relationships; and 4) document network visualization. Fig. 1 provides an overview of the methodology.

2. Description

2.1. Research questions and selection of eligible documents

Step 1 includes the development of research questions, systematic document search, document categorization, and data extraction. As in all research activities, the development of a research question initiates the process. In the case of this methodology, perspectives from systematic reviews and bibliometrics inform the research questions. Two key research questions define this step of the methodology 1) Original research—What is the clinical evidence base of the original research? and 2) Context—How is this evidence represented in different types of documents?

To understand the primary evidence base of original research, develop systematic review research questions, addressing a specific patient's population, intervention, comparison, and outcomes [10]. We suggest including clinically important, patient-centered outcomes representative of benefit, harm, and quality of life [11]. This may vary as a function of clinical condition and nature of the inquiry and is driven by the research questions.

To understand the relationships between related documents and the original research, develop research questions similar to a bibliometric review, addressing what type of

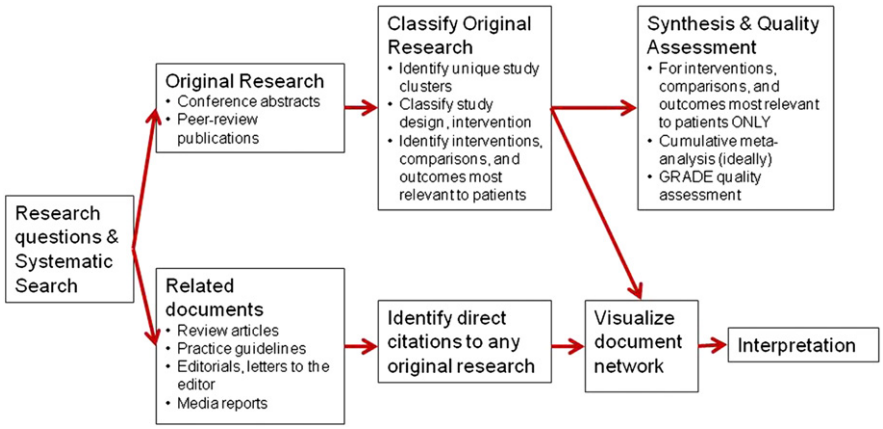


Fig. 1. Overview of key *s*ystematic *r*eview and *b*ibliometr*ic* *n*etwork *a*nalysis (SeBriNA) steps. In this figure, we outline the key steps to conduct a SeBriNA.

documents are available that relate to the original research and the nature of these relationships [8]. For example, to understand the relationships between media reports and original research, a sample research question is, "*How do media reports cite original research?*"

A priori, we suggest defining the scope of documents for the review. For example, we defined a document as a "written record, including published and unpublished material" [8]. We suggest considering the range of original research to include the perspective of research design (RCT, observation studies, etc.) and format of publication (e.g., full publication and/or abstracts and/or conference presentation slides that are publicly available). Examples of related documents include reviews (systematic or narrative), clinical practice guidelines, editorials, and media reports. Throughout this article, we use the term "document" to represent the smallest unit of analysis of any of the foregoing reports. For example, although a systematic review may include several original research studies, the systematic review counts as one document. We suggest deliberate decisions regarding inclusion criteria because of the increase in complexity and work required to execute the methodology.

To identify potentially relevant original research and related documents, the SeBriNA uses search methods based on a systematic review [12]. We suggest consulting health science librarians and information specialists familiar with each document source for guidance to develop search strategies. To efficiently manage the volume of citations, we suggest using electronic reference management software (e.g., EndNote) and developing an electronic relational database (e.g., Microsoft Access) for further data management. To minimize bias, and manage document volume among reviewers, conduct a two-stage review process independently, in duplicate, noting exclusion reasons. First, review *all* documents by title and abstract, coding each as "include," "exclude," or "not sure," and retrieve the full text of all documents coded as either "include" or "not sure" for further review. Next, review all full-text documents, coding each document as "include" or "exclude." Discuss all disagreements, and resolve all differences by consensus. As a measure of inter-rater reliability, calculate the Kappa statistic (K) and the 95% confidence interval [13,14]. One method of interpreting reliability coefficients is as follows: slight, 0.0−0.20; fair, 0.21−0.40; moderate, 0.41−0.60; substantial, 0.61−0.80; and almost perfect, 0.81−1.00 [15].

2.2. Original research data extraction and analysis

From the cohort of included documents, identify core characteristics of original research and related documents. Next, organize the original research documents into unique study clusters, determine the cumulative quality of the evidence over time, and assess the overall quality of evidence by outcome.

Similar to a systematic review, identify basic characteristics of all documents, such as document type, publication source, publication date, and author. For original research, document clinical and methodological characteristics such as study design, intervention, sample size, estimates of effect, risk of bias attributes (e.g., adequacy of randomization; allocation concealment; and blinding of participants, caregivers, and outcome assessors), funding source, and author affiliation with industry. Identify additional characteristics of related documents as needed, based on the research question for each document.

Using original research documents, identify study clusters, and describe the characteristics of study clusters. We defined a "study cluster" as a metric to describe how one original research study may present different results and outcomes in a series of separate publications and forms over time. We identified study clusters by matching the authors' descriptions of the study sample and intervention [16]. For example, over time, an RCT may appear as both a conference abstract and as a peer-review publication: preliminary results as a conference abstract; safety results as a separate conference abstract; an interim analysis of survival as a conference abstract; and a peer-review

publication of final results of response, safety, and survival. In this example, the study cluster includes four documents: three conference abstracts and one peer-review publication. Use simple descriptive statistics to determine the dispersion of the number of documents per study cluster and categorize study clusters by intervention and study design. Focusing on randomized trials, conduct further analyses on study clusters with similar interventions.

Where possible, determine the evolving quality of the evidence over time using cumulative meta-analysis (e.g., by year, by decade). Repeat the following process for each time period: first, calculate the estimate of effect of the accumulated evidence for each outcome [17]. By time period, represent each study cluster once for each cumulative meta-analysis estimate of effect, and use accepted methods to assess heterogeneity [18] and publication bias [12]. Next, for the same time period, determine the overall quality of evidence by outcome and across outcomes using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach, which assesses the quality of evidence, considering risk of bias, consistency of results, directness of comparisons, precision, and publication bias [19].

2.3. Document network relationships

In this step, we document two relationships: 1) within original research, for each study cluster among original research documents, and 2) between original research citations and related documents. This allows us to identify highly cited original research documents. First, document all original research within the study clusters in step 2 (above). Next, conduct a direct citation analysis between related documents and all original research documents [8], by examining the reference lists of related documents and identifying citations in the original research cohort. For example, to relate original research to systematic reviews, identify direct citations from the documents meeting inclusion criteria of the systematic review to the original research cohort. Document all relationships in a matrix, determine the number of citations by each original research document, and conduct a descriptive analysis of the relationships between original research and related documents.

2.4. Document network visualization

In this last step, visually organize and present the data, using space, symbols, and color to represent each document in a network figure similar to a scatterplot. In the network figure, link the relationships within original research study clusters, and between citing documents and original research (from step 3). Juxtapose the data visualization against the cumulative meta-analysis and assessment of the quality of evidence by outcome (from step 2).

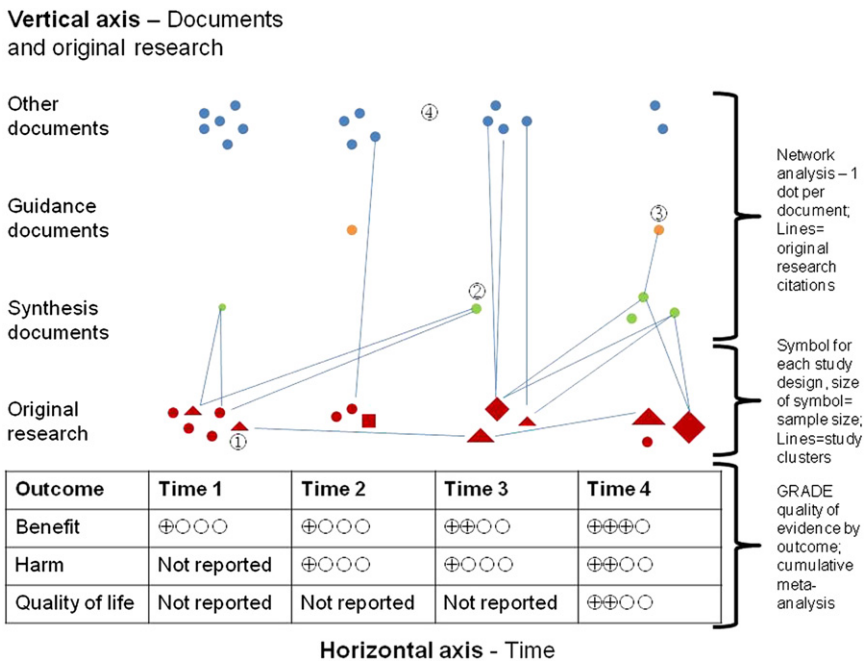
To organize and visually represent the data, consider key attributes of the documents, using space, size, symbols, and color to communicate multiple attributes of each document, plotting all documents. For example, use the horizontal axis (individual columns across the graph) to represent the year of presentation, and the vertical axis (rows) for different document types. Within documents, use symbols to highlight specific attributes, such as study design (e.g., diamonds for randomized trials, larger diamonds represent larger sample sizes), and use color to reinforce differences and importance among document types (e.g., gray for gray literature, red for peer-reviewed literature).

Next, graph the network relationships. We suggest using social network analysis software to develop the document network matrix and attributes (e.g., UCINET for Windows, Analytic Technologies, Lexington, KY), and social network graphics packages (e.g., NETDRAW, Analytic Technologies, Lexington, KY) to manage large volumes of data. Finally, juxtapose the estimates of effect and quality of evidence beneath the network analysis diagram for further analysis and interpretation. Fig. 2 presents and describes a schematic of the single figure from a SeBriNA. For a detailed example of the network visualization, please see the accompanying article outlining the application of this methodology to rituximab for non-Hodgkin's lymphoma.

3. Discussion

In this article, we outline the steps of a new methodology, the SeBriNA. This methodology addresses a gap in the existing literature by allowing us to integrate, interpret, and visually cross-reference documents citing original research against the current state of the evidence. Grounded in two established methodologies, systematic reviews [7] and bibliometrics [8,9], the SeBriNA transparently contextualizes evidence on patient-centered comparisons and outcomes within a larger network of related documents. It focuses on the fundamentals of study design and study execution and how these factors impact our confidence in the estimate of effect for a treatment. By juxtaposing the quantity, quality, and consistency of patient-centered outcomes over time, across various evidence and information sources, the SeBriNA can facilitate more transparent methodological discussions about the strengths and weaknesses of original research evidence in a new health care technology. In our companion paper in this issue, we apply the SeBriNA methodology to rituximab for non-Hodgkin's lymphoma.

Strengths of this methodology include comprehensiveness and reproducibility of included documents, inclusion of gray literature, documented decision rules, and visual representation of the document network. We suggest a transparent and rigorous methodology for each step, grounded in the systematic review and bibliometric analysis traditions. Through these steps, evidence consumers can have confidence in the reproducibility and comprehensiveness of included documents and can review the rationale underpinning subjective judgments.



Outcome	Time 1	Time 2	Time 3	Time 4
Benefit	⊕○○○	⊕○○○	⊕⊕○○	⊕⊕⊕○
Harm	Not reported	⊕○○○	⊕○○○	⊕⊕○○
Quality of life	Not reported	Not reported	Not reported	⊕⊕○○

Fig. 2. Schematic representation of systematic review and bibliometric network analysis (SeBriNA). The horizontal axis represents time, and the vertical axis represents different documents. In this exemplar, we included original peer-review research, synthesis documents (e.g., review articles), guidance documents (e.g., clinical practice guidelines), and other documents (e.g., media reports). The table represents the cumulative meta-analysis and quality of evidence for outcomes of interest over time. The symbols within the table represent the overall quality of the evidence for each important outcome (⊕○○○ = very low quality evidence; ⊕⊕⊕⊕ = high quality evidence). Across document types, represent each document in the figure, by publication year. Within original research, we chose symbols to represent study design (e.g., diamonds, ◆ = randomized controlled trials [RCT]; upward triangles, ▲ = case series; circles, ● = case report; symbol size = study sample size). ① = study cluster. Lines connect the three upward triangles of multiple reports of the same study. ② = citation relationships between review articles and original research. Note the varying types of original research cited by different review articles. ③ = citation relationships between guidance documents and original research. Note how one guidance document cites no research from the original research cohort, whereas the other cites a review. ④ = citation relationships between media reports and original research. Note the different types of research designs cited by media reports, many media reports citing the first RCT, one media report citing a case study (Time 2), and some media reports citing no original research.

Our methodology allows evidence consumers to look at the totality of the body of research evidence. By visualizing the document network, all evidence consumers have a common starting point for methodological discussions about the scientific evidence and how other documents represent the evidence. We suggest the document network is a helpful addition to existing evidence synthesis tools such as evidence tables, because it juxtaposes evidence quantity against evidence quality. Outputs from the SeBriNA may help inform or explain funding and access decisions.

The methodology also has limitations. The comprehensiveness of the data visualization graphic may distract evidence consumers from focusing on the most relevant evidence for decision making, however, we envision this methodology as a *complement* to existing evidence summary tables. The methodology is resource intense, examines only citation relationships, and does not include economic evaluations or qualitative research. Because the methodology is comprehensive, executing the methodology is potentially resource intense. Although original research evidence data are global, clinical or policy decisions are more local. Thus, we suggest that international collaboration on evidence synthesis and document citation may reduce the burden of human resources, and facilitate timely data acquisition.

Although the SeBriNA examines citation relationships, it does not study how the documents cite the original research evidence. A citation may be supportive, neutral, critical, or misrepresent the original research [20]. The SeBriNA links the related documents to the original research, providing the necessary first step to conduct further content analysis. Building on the strengths of the SeBriNA, content analysis could provide further insights about the incremental contributions of synthesis documents such as reviews and guidelines, or study the sensationalism or hype of media reports. Finally, in this first iteration of the SeBriNA, we excluded economic evaluations and qualitative research. We chose to focus on original research data and suggest future iterations consider integration of economic evaluations and qualitative research into the document network.

We believe the foundation of this methodology offers opportunities for creativity and innovation to improve our understanding of how we use evidence, and meaningfully engage evidence stakeholders in discussions about the use of evidence. Because of the complexity and abundance of original research evidence and its varied representation by different documents, we suggest the SeBriNA is a synthesis tool to facilitate methodological discussion of the evidence underlying a new health care technology, especially in

expensive or controversial technologies. For other diseases, technologies, and populations, researchers may consider other types of documents to further contextualize original research, such as Web sites from patient's advocacy groups, regulatory approval submissions, or policy decisions from different jurisdictions.

Returning to the introduction, we demonstrate the potential value of the SeBriNA. For the media reports relating autism to pediatric vaccinations, juxtaposition of scientific evidence against media reports from the SeBriNA could facilitate more deliberate discussions about the available scientific evidence among advocacy groups, clinicians, researchers, and policy makers. For example, we could link the media reports to the original research studies to see if one study was more highly cited than another, or determine whether different citation patterns occurred between review articles and original research.

4. Conclusions

With an increasing imperative to incorporate evidence-informed decision making into clinical and policy decisions of new health care technologies, we propose the SeBriNA as a methodology to visually contextualize and interpret relationships between original research data and documents related to the original research. Built on the strengths of two rigorous methodologies, systematic reviews and bibliometric analyses, the SeBriNA provides a generalizable and common starting point for evidence consumers to discuss methodological concerns salient to a new health care technology and representation of the evidence. Applications of this methodology include support for clinical and policy decisions, and identification of research gaps. We need further research to integrate content analysis, economic evaluations, and qualitative research within the document network and understand the utility and acceptability of this methodology by evidence consumers.

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