

Future of evidence ecosystem series: 1. Introduction — Evidence synthesis ecosystem needs dramatic change

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Abstract (199/200 words)

To make healthcare decisions, patients, clinicians, clinical practice guideline developers, researchers, policy-makers and health system managers need a comprehensive, critical, accessible, actionable and up-to-date synthesis of all available evidence in a given condition.

Systematic reviews and meta-analyses are a cornerstone of healthcare decisions. However, despite the increasing number of published systematic reviews of therapeutic interventions, the current evidence synthesis ecosystem is not properly addressing stakeholders' needs.

The current production process leads to a series of disparate systematic reviews due to erratic and inefficient planning with a process that is not always comprehensive, and is prone to bias.

Evidence synthesis depends on the quality of primary research, so primary research that is not available, is biased or selectively reported raises important concerns. Moreover, the lack of interactions between the community of primary research producers and systematic reviewers impedes the optimal use of data.

The context has considerably evolved, with ongoing research innovations, a new medical approach with the end of the one-size-fits-all approach, more available data, and new patient expectations. All these changes must be introduced into the future evidence ecosystem.

Dramatic changes are needed to enable this future ecosystem to become user-driven and user-oriented and more useful for decision-making.

Keywords: systematic review, meta-analysis, evidence synthesis ecosystem, decision-making

What is new?

- The planning, coordination and conduct of systematic reviews is currently insufficient.
- There is limited interaction between the primary research enterprise and the evidence synthesis enterprise, which impedes their mutual improvement.
- The evidence synthesis ecosystem results in a fragmented picture of available evidence and hampers providing useful information for health decision making.

Introduction

Results of more than 30 000 new randomised controlled trials (RCTs) are published every year [1]. Hence, patients, clinicians, clinical practice guideline developers, researchers, policy-makers, health system managers and funders alike find it extremely challenging to consider all the primary research findings on a given topic when making healthcare decisions [2]. They need a comprehensive, critical, up-to-date synthesis of all available evidence about the efficacy and safety of interventions. Accordingly, systematic reviews (i.e., a systematic identification, appraisal, and synthesis of all relevant prior studies on a specified topic according to a predetermined and explicit method [3] and meta-analyses (i.e., the statistical aggregation of all relevant prior studies [3] are a cornerstone of healthcare decisions [4,5].

Systematic reviews of RCTs have been developed to address this need and are usually considered the highest in the hierarchy of medical evidence [6]. The number of systematic reviews and meta-analyses published is increasing exponentially, with currently more than 10 000 meta-analyses published every year and involving tens of thousands of researchers [1,7].

Despite this tremendous amount of work, the current evidence synthesis ecosystem — ecosystem for producing systematic reviews, meta-analyses and network meta-analyses — is not properly addressing stakeholders' needs. There is an urgent need to fully rethink evidence synthesis and develop new and better approaches that match the needs of evidence users more closely.

In this series, we discuss the limitations of the current system of evidence synthesis for therapeutic interventions (paper 1), discuss new methods (paper 2) and propose a new ecosystem (paper 3) (Box 1).

Box 1: Overview of the future of evidence ecosystem series

Future of evidence ecosystem series: 1. Introduction — Evidence synthesis ecosystem needs dramatic change

Authors: Isabelle Boutron, Perrine Créquit, Hywel Williams, Joerg Meerpohl, Jonathan C. Craig, Philippe Ravaud

Description: The authors present why the planning, conduct and reporting of systematic reviews and meta-analyses of therapeutic interventions is suboptimal, leading to duplication and gaps in evidence synthesis with flawed systematic reviews. Then, they discuss how the context and the needs for systematic reviews have evolved considering innovations in healthcare, changes in community expectations and the evolution of primary research and current knowledge. They demonstrate why the evidence synthesis ecosystem needs to change.

Future of evidence ecosystem series: 2. Current opportunities and need for better tools and methods

Authors: Perrine Créquit, Isabelle Boutron, Hywel Williams, Joerg Meerpohl, Jonathan C. Craig, Philippe Ravaud

Description: The authors present all existing sources of data, detailing the most recent ones, such as clinical study reports, individual patient data and large-scale routinely collected data. They present new methods of evidence synthesis, “living” systematic reviews and living network meta-analyses as well as new approaches and tools to sustain this new evidence synthesis framework.

Future of evidence ecosystem series: 3. From an evidence synthesis ecosystem to an evidence ecosystem

Authors: Philippe Ravaud, Perrine Créquit, Hywel Williams, Joerg Meerpohl, Jonathan C. Craig, Isabelle Boutron

Description: The authors discuss the need to rethink the evidence synthesis ecosystem, its infrastructure and management, and to move toward an evidence ecosystem that produces “living” evidence syntheses. They explain how this new evidence ecosystem should bridge the gaps between evidence synthesis communities, primary researchers, clinical practice guidelines developers, regulatory authorities, and decision-makers.

1. The planning, conduct and reporting of systematic reviews and meta-analyses of therapeutic interventions is suboptimal

Despite the rapid increase in number of published systematic reviews of therapeutic interventions, their planning, conduct and reporting raises important concerns, and their value is being widely questioned [7,8].

1.1.Duplication and gaps

Overall, the planning of systematic reviews and meta-analysis is haphazard, with evidence of redundancy, wasted efforts and important gaps [9,10]. A meta-epidemiologic study showed that 67% of systematic reviews contained at least one partially or completely overlapping meta-analysis with another systematic review [10]. Purposeful replication (using the same data with the same or updated methods) may have a role in testing the validity of previous results, but the overlapping meta-analysis observed was not purposeful [10]. Cochrane has attempted to reduce duplication with a process whereby priorities are identified and titles registered before the review is conducted.

Furthermore, instead of considering all treatments available for a given condition, most systematic reviews and meta-analyses have narrow scopes and focus on specific agents [11]. For example, the whole set of systematic reviews of second-line treatments for advanced non-small-cell lung cancer published each year from 2009 to 2015 incorporated only 40% of the interventions and trials available [12].

In addition, most systematic reviews and meta-analyses focus on efficacy and neglect safety. For example, in a sample of 78 gastroenterology systematic reviews, one third never mentioned the harms of the intervention anywhere in the article, and less than half included adverse events as an outcome measure [13].

Finally, the current “staccato” method of performing systematic reviews means that they are always out of date (and some by a long margin) when they are published. An estimated 23% of reviews are out of date after 2 years and 70% after 10 years [14].

For a given condition, the current global haphazard process leads to a series of disparate systematic reviews in terms of selection criteria, methodological quality, search dates, and overlapping scope. This situation results in a fragmented picture of available evidence and hampers providing useful information for health decision-making.

1.2. Systematic but flawed

The label “systematic review” is not in itself a guarantee of quality [8]. The methods used to conduct systematic reviews are frequently flawed [15]. The search strategy is rarely comprehensive [12]. In a random sample of 300 systematic reviews, only 7% searched for sources of unpublished data [15]. Among a sample of 223 systematic reviews, half did not report a search of trial registries [16]. Data extraction also raises important concerns, with high inter-observer variation for extraction of outcome measures due to differences in the selection of time points, scales, control groups, type of calculations, and errors [17]. The assessment of the risk of bias of a primary study is often inconsistent and frequently not considered in the interpretation of results [15,18], and reporting bias is often ignored when interpreting the findings of a systematic review [15,19]. Furthermore, the current “best practice” methods are themselves increasingly recognized to be insufficient. Despite the publication and endorsement of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement by several journals [20–23], the reporting of systematic reviews remains incomplete [24]. Reproducible research practices such as sharing data and statistical code are underused [25,26].

In essence, even with prospective registration of protocols, systematic reviews rely on a retrospective process, at least in part. There remains a risk of “cherry picking.” For example, decisions to include or exclude a study in the systematic review or meta-analysis and choices on which outcome measures should be extracted when several measures are available (i.e., different time points, metrics, data sources) [27] could be affected by awareness of the study results. To limit this risk, a review protocol must be developed *a priori* and be available with the final review publication. The Prospective Register of Systematic Reviews (PROSPERO) has been developed (<https://www.crd.york.ac.uk/prospero/>). However, only a limited number of systematic reviews are registered: in a 2016 cross-sectional study, only 4% (12/300) had been prospectively registered [15]. Furthermore, studies comparing published reviews to their protocols or registered records showed important changes in the methods used and discrepancies in primary outcomes in 20% to 47% of the reviews [28–30].

Finally, the reliability of results from systematic reviews and meta-analyses performed by pharmaceutical companies, or researchers linked to these companies, has been questioned [31]. Conflicts of interest can affect systematic reviews. A systematic review comparing conclusions of meta-analyses performed by industry versus non-industry showed that financial ties to one drug company was the only characteristic significantly associated with favorable conclusions [32]. Some professional contracting companies are investing in the research synthesis enterprise, particularly those commissioned by industry for performing network meta-analyses [33].

1.3. Deficiencies in primary research

Evidence synthesis depends on the quality of primary research. Particularly, reporting bias, poor reporting of primary studies, and poor quality of primary studies raise important concerns. Unfortunately, primary research is often not available, is biased, and is selectively

or incompletely reported [34–37]. Selective reporting of statistically significant clinical trials and outcomes is frequent. About 50% of RCTs are never published [38]. In a study of cancer research, results of nearly half of trials performed in the United States were not publicly available 3 years after trial completion [36]. Such reporting bias leads to unrealistic and misleading estimates of drug effectiveness [34,35,37,39]. For example, a study in the field of depression comparing results of trials submitted to the US Food and Drug Administration (FDA) to published trials found that results for 31% of trials were not published, which resulted in an average increase in effect size of 32% overall [39]. Flaws in the design, conduct, and analysis of RCTs can also bias effect estimates [40–45] and lead to erroneous conclusions [46]. A large meta-epidemiologic study of RCTs included in Cochrane systematic reviews showed that 43% of the RCTs had at least one domain at high risk of bias [47]. A study of Cochrane systematic reviews incorporating a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment showed that only 19% had at least one outcome with high quality of evidence [48]. Pharmaceutical companies fund most clinical trials [49]. However, some evidence suggests that the planning and reporting of such trials can raise important issues [50,51].

Despite initiatives to identify and agree on critically important outcomes and their corresponding instruments to be reported in all RCTs, such as Outcome Measures in Rheumatology (OMERACT) [52] and Core Outcome Measures for Effectiveness Trials (COMET) [53], outcomes assessed in RCTs feature high heterogeneity [54]. Outcomes that are not measured, are measured differently or are not reported hampers the optimal conduct of meta-analyses. For example, half of RCTs assessing second-line treatments for advanced non-small-cell lung cancer reported the number of serious adverse events and one fifth quality of life [55]. Similarly, only 26% of trials assessing non-opioid analgesics in adults after major surgery reported serious adverse events [56]. A systematic review of RCTs of schizophrenia

over 60 years identified 2194 different rating scales to measure outcomes [57]. In a study of RCTs included in Cochrane systematic reviews, 63% had at least one important outcome missing [54]. Another study of dermatology systematic reviews and their included trials found a small overlap between review and trial outcomes, rendering any form of meta-analysis impossible for 48% of primary review outcomes [58].

1.4.The disconnect between the global enterprise of evidence generation and synthesis

Currently, research involves two research enterprises: the primary research enterprise and the evidence synthesis enterprise. Surprisingly, the two have limited interaction, and they appear to be largely disconnected despite calls that trials should begin and end with systematic reviews of relevant evidence [59]. Systematic reviewers mainly contact trialists to obtain individual participant data, non-reported outcome data or information on how the trials were conducted to evaluate the risk of bias but do not provide feedback to trialists to help them improve their trial or plan future trials. Trialists rarely rely on existing systematic reviews to plan their trials [35]. They do not choose their comparator, determine their sample size [60] or choose their outcomes guided by the ultimate goal of being included in a future meta-analysis to impact decision-making. When the trial is completed, they rarely inform or share their results with systematic reviewers for updating existing systematic reviews [61–63]. Of course, a deep collaboration between reviewers and trialists could also have potential downsides if it undermines the perceived equipoise and dispassionate nature of the systematic reviews (i.e. some trialists may have strong convictions and sometimes even conflicts of interest that prevent the impartiality required to conduct evidence syntheses). Nevertheless, the current system in which both enterprises function independently and in parallel without any coordination is an important source of avoidable waste.

Furthermore, most evidence synthesis considers only randomized trials even though this design has limited external validity. Evidence from observational studies as well as routinely collected data (i.e., electronic medical records, administrative and claims databases), are increasingly available. Such evidence can be very valuable for evaluating treatment benefit and harm in “real life”. For some clinical questions, observational data are even the only source of evidence (e.g. surgery, long-term follow-up). However, inclusion of observational studies in systematic reviews creates a number of significant challenges to the process of production.

In addition, the whole evidence synthesis enterprise may not be adequately configured to meet the needs of stakeholders. The planning and conduct of a systematic review is usually a one-shot process, whereby a systematic review team decides to answer a clinical question at an arbitrarily chosen point in time on an ad-hoc basis without any consideration of the broad panorama of all available evidence and without any planning for updates. Therefore, numerous systematic reviews are outdated with the rapid accumulation of new trials [14,64,65]. There are also challenges beyond simply identifying new data — in particular the effort required to introduce changing methods.

This lack of prioritization and defined scope in the current landscape of evidence synthesis results in important overlaps and gaps [10,66–68]. The creation of PROSPERO is useful for understanding the landscape of research synthesis but insufficient because registration is not mandatory, and whether the registration was prospectively performed cannot be determined [69].

Finally, the rigorous methodology of systematic reviews is inherently time-consuming and burdensome [70]. For example, the median time to publication of Cochrane review is 2.8 years (range 1 to 8) [70]. This delay between planning and publication and lack of an organized updating process is difficult to accept for end-users who often need to make

immediate and informed decisions. There is a difficult trade-off decision between quality, time to results availability and resources.

Over the last 20 years, Cochrane, the international collaboration dedicated to evidence synthesis of interventions, has made major achievements to develop and strengthen the field of evidence synthesis. For example, Cochrane has tried to take control of a profusion of haphazard reviews by ensuring some degree of prioritization according to stakeholder needs, avoiding overlap by circulating newly registered titles among groups. Furthermore, Cochrane has been pioneering most of the methods, developing the Cochrane Handbook and providing access to the most-used software for systematic reviews and meta-analyses (Revman), among other innovations. Cochrane is also working on specific approaches to counterbalance the one-shot nature of most systematic reviews and ensure that systematic reviews are regularly updated. However, Cochrane cannot control the global systematic review production, and most reviews are produced outside of Cochrane. Indeed, only 15% of systematic reviews were Cochrane in 2014 [14].

2. Context and needs for systematic reviews has evolved considerably

2.1. Healthcare is evolving rapidly

With ongoing research innovations, usually several alternative drugs and non-drug complex interventions (e.g., behavioral interventions, education, surgery, psychotherapy) are now available to treat a given clinical condition. Most of these treatments have been assessed in two-arm RCTs comparing the new treatment to a placebo or, less commonly, to an active comparator. For instance, about 50 second-line non-small-cell lung cancer treatments have been assessed [55]. Consequently, patients, clinicians, and health decision makers are not interested in a single comparison of two treatments — they want to know which treatments

among all existing treatments are the most beneficial in terms of a trade-off between benefits and harms.

Medicine is also evolving. The “*one-size-fits-all*” approach that aims to demonstrate that a treatment is beneficial on average for patients with a given medical condition is being questioned. New approaches being explored include the “*precision- or stratified-medicine*” approach, which aims to determine the most effective treatment for a given patient considering all genetic, environmental, and lifestyle factors. Systematic reviews and meta-analyses as they are currently being conducted are not meeting these needs. They provide an average treatment effect, focus on comparing two treatments and currently do not assess who will benefit from treatment or be harmed by treatment.

2.2. The community has changed

Patients’ expectations are also changing. They want to be actively involved in the planning, conduct and reporting of clinical research and to move to clinical research carried out “with or by members of the public rather than to, about or for them” (<https://www.peopleinresearch.org/public-involvement/>) [71]. Patients are gathering in large patient communities. These communities can have considerable impact, as demonstrated by the *AllTrials* initiative (<http://www.alltrials.net>), which is calling for all clinical trials to be registered and summary results reported.

There have also been important changes in paradigm for research funding to be more connected to final users’ needs. For example, the Patient-Centered Outcomes Research Institute (PCORI) in the United States aims to fund research that focuses on patient-centered outcomes (i.e., research questions and outcomes that are meaningful for patients). The Canada Strategy for Patient-Oriented Research (SPOR) initiative aims to engage patients, their caregivers, and families as partners in the research process. Their ambition is to help

transform the role of patient from a passive receptor of services to a proactive partner who helps shape health research and, as a result, health care.

2.3. Access to primary research data is evolving

Currently, systematic reviews mainly consider summary data extracted from published articles of RCTs. Concomitant with an increase of about 2.5% each year in published scientific articles, the characteristics of primary research are evolving considerably.

In addition, the landscape of clinical research dissemination is changing substantially, with several initiatives aimed at increasing access to all trial results and to individual participant data. The 2007 FDA Amendments Act requires that trial results be posted on a clinical trial registry within 1 year after study completion, and registries are now an essential source of data. For example, a study showed that in 43% of reviews, unpublished trials could be identified in trial registries, with results available in the registry for half of them [16]. Furthermore, reporting of serious adverse events is significantly more complete at ClinicalTrials.gov than in published articles [38]. Pharmaceutical companies have set up a platform (<https://www.clinicalstudydatarequest.com>) for investigators to access all information from the protocols to the clinical study report and individual participant data [72]. Other initiatives, such as the Yale University Open Data Access Project (<http://yoda.yale.edu>), aim at increasing access to clinical research data [73]. Since 2015, the European Medicines Agency (EMA) has provided access to clinical study reports submitted to the agency. Access to all this documentation and to participant data represents a real opportunity to meaningfully reanalyze, reuse and incorporate data in systematic reviews but also makes the process more complex, time-consuming and costly, with several challenges to overcome. This increased transparency and availability of data begins to address the realization over the past 2 decades that reliance on the data provided in short reports of RCTs in scientific journals is markedly

prone to bias because of selective outcome reporting. Furthermore, it illustrates that very limited and cursory efforts have been made toward dissemination and knowledge translation. Paper 2 explores in more detail solutions to these issues [74].

Finally, with the abundance of available data (e.g., routinely collected data, electronic health records, medico-administrative data) and the development of new statistical methods and designs for approaching causality (e.g., emulating trials by using propensity scores [75], Mendelian randomization, regression discontinuity designs [76]), observational data are becoming an increasingly more powerful source of information for comparative effectiveness research. These data can contribute to evaluating interventions in a real-life context, at lower cost and faster. Nevertheless, these data are rarely considered in systematic reviews and meta-analyses, and their inclusion raises specific methodological challenges [77].

2.4. Knowledge has changed

New empirical evidence has shown that treatment effects vary by factors such as the sample size [78], diversity between trial settings (study location) [79], domains of risk of bias [80], time when trials are performed (older vs recent trials) and type of interventions [81]. Furthermore, patients and clinicians are not interested in an average treatment effect combining results of studies performed in various populations and settings but rather in a more individualised approach. Therefore, focusing on estimating an average treatment effect across all trials can be questionable particularly when the intervention is performed in very different contexts, with patients cared for in very different ways [82]. Finally, most systematic reviews focus on the treatment effects, and safety is neglected.

Conclusion

The current evidence synthesis ecosystem is not sufficiently user-driven and user-oriented and thus does not address stakeholders' needs, the interaction with community of primary research producers to enable optimal use of data is lacking, and the planning, coordination and conduct of systematic reviews is insufficient. Dramatic changes are needed to improve the system so that it becomes more useful to the decision-making process. In the second article of this series, we explore new tools and methods available and needed for implementing these changes [74]. In the third article, we propose a paradigm shift to move our ecosystem toward an Evidence Ecosystem that produces “living” evidence syntheses [83].

As highlighted by Bastian, Glasziou and Chalmers, “given the triple constraint posed by the growth in trials, the increasing complexity of review methods, and often limited resources, Archie Cochrane’s vision will not be achieved without some serious changes” [1].

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