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

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Abstract (200 words/200)

To become user-driven and more useful for decision-making, the current evidence synthesis ecosystem requires significant changes (Paper 1.Future of evidence ecosystem series). Reviewers have access to new sources of data (clinical trial registries, protocols, clinical study reports from regulatory agencies or pharmaceutical companies) for more information on randomized control trials. With all these new available data, the management of multiple and scattered trial reports is even more challenging. New types of data are also becoming available: individual patient data and routinely collected data. With the increasing number of diverse sources to be searched and the amount of data to be extracted, the process needs to be rethought. New approaches and tools, such as automation technologies and crowdsourcing, should help accelerate the process. The implementation of these new approaches and methods requires a substantial rethinking and redesign of the current evidence synthesis ecosystem. The concept of a "living" evidence synthesis enterprise, with living systematic review and living network meta-analysis, has recently emerged. Such an evidence synthesis ecosystem implies conceptualizing evidence synthesis as a continuous process built around a clinical question of interest and no longer as a small team independently answering a specific clinical question at a single point in time.

Keywords: systematic review, evidence synthesis, clinical study report, automation, crowdsourcing

What is new?

- Access to new sources and types of data and recent developments of methods, technologies and tools create additional challenges as well as opportunities to achieve a better-designed ecosystem to support the production of high-quality evidence syntheses.
- Multiple reports for a trial require assessing the validity of the data and exploring appropriate methods to define whether and how these data should be included in systematic reviews.
- The implementation of these new approaches and methods requires rethinking the current evidence synthesis ecosystem as a living evidence synthesis enterprise and no longer a one-shot process.

As presented in paper 1 of the Future of evidence ecosystem series, the current evidence synthesis ecosystem ─ ecosystem for producing systematic reviews, meta-analyses and network meta-analyses ─ requires significant changes to overcome its important drawbacks, to adapt to developments in health care and primary research and become more useful in the decision-making process.

In this paper, we will consider how access to new sources and types of data and recent developments of new methods, new technologies, and new tools presents a great opportunity to create and sustain an ecosystem that is better designed to support production of updated high-quality evidence syntheses.

1. Using all existing sources and types of data

1.1. Searching, using, comparing and integrating all sources of data

As previously discussed in paper 1, most systematic reviews currently rely on summary data extracted from reports published in peer-reviewed journals or reported in conference abstracts. This approach raises important concerns related to reporting bias [1–4] and lack of transparency [5–9]. In contrast, under pressure from editors, funders, patient and public initiatives, and regulatory authorities, new sources of data are now increasingly available. These new sources of data allow reviewers to obtain more information on the methodology of randomized controlled trials (RCTs) as well as their results through aggregated data.

Clinical trial registries:

Clinical trial registries such as ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform (WHO-ICTRP), and the European Union Clinical Trials Register (EU-CTR) have become important sources of information for

systematic reviewers. Such registries allow for identifying unpublished trials if these trials were initially registered as required by many authorities. They can be used to identify outcome reporting bias (e.g., change in the primary outcome) because information on the primary and secondary outcomes is included in the registration record before the start of the study [10]. Furthermore, theoretically, one should be able to access summary results of trials including at least one site in the United States or European Union. Indeed, by law, the section 801 of the 2007 US Food and Drug Administration (FDA) Amendment Act (FDAAA), requires all sponsors/investigators of clinical trials of drugs, biologics, and medical devices regulated by the FDA with at least one site in the United States to post their results at ClinicalTrials.gov within 1 year after trial completion. The US National Institutes of Health, the major US funder of academic trials, enforces this policy for all trials they fund, whether subject to FDAAA section 801 requirements or not. In 2014, the European commission on clinical trials directive required mandatory posting of results for any interventional trials registered in the European Clinical Trials Database (EudraCT). Currently, the results of 36,751 trials are available at ClinicalTrials.gov [11] and 12,235 at EudraCT [12]. However, compliance with these laws and policies is suboptimal, with 40% of trial results not posted according to the FDAAA Trial Tracker (http://fdaaa.trialstracker.net) and half according to the EU Trials Tracker (http://eu.trialstracker.net/) [13,14].

Clinical trial registries can be extremely valuable for systematic reviewers because the results of these recent trials are frequently not published at the time of posting [15] and because the completeness and detail of reporting may be higher when results, particularly safety data, are posted rather than reported in a published journal article [16].

Despite often more detailed data available in trial registries, usually only limited information related to the methods used and analyses performed is available; the description of outcomes

is often vague and the randomization process is only rarely described [17,18]. To overcome this limitation, ClinicalTrials.gov has now made it possible to upload the protocol and statistical analysis plans. Moreover, discrepancies in the data reported in trial registrations and their publications are common [19].

Specific journals, and appendices to journal publications:

Protocols can also be available as published articles — journals such as *Trials* were developed specifically to publish protocols — but also as appendices of journal publications as now systematically requested by an increasing number of journals (e.g., *New England Journal of Medicine*, *Journal of Clinical Oncology* or *Annals of Internal Medicine*).

Regulatory agencies:

Regulatory agencies such as the US FDA and European Medicines Agency (EMA) also give access to some additional information for the drugs they approved. The FDA shares the reviews and related documents on Drugs@FDA, but the trial protocol, clinical study report (CSR), case report forms and individual patient data (IPD) are not routinely available [18,20,21], despite the fact that the FDA has released CSRs and other documents on a voluntary basis since 2018. Since 2015, via a specific website (https://clinicaldata.ema.europa.eu/web/cdp/home), the EMA has given access to the CSRs submitted to the agency by companies in support of their marketing authorization applications. However, these documents are often thousands of pages long and necessarily take more time to analyse than reading a traditionally published article, which is usually a few pages long. For example, the compression factor (i.e., ratio of number of pages of the CSR to the published article) of a sample of CSRs obtained from public sources ranged from 1 to 1221 [20]. Some issues related to the large redaction of some of these documents were also

raised [20]. Nevertheless, CSRs should be highly structured, and data presented are more complete in terms of efficacy, safety, and methodology and bias assessment [18,20]. Furthermore, with some training, the clear structure and complete reporting of information in CSRs allows for data extraction in an acceptable time frame and easier than finding it in multiple trial reports. However, considering CSRs as a source of data for inclusion in systematic reviews raises some issues [20,22,23]. First, access to these data is limited and requesting the data involves excessive time. Second, CSRs are long and complex documents containing a very large amount of information, which is time-consuming and resource-intensive work for systematic reviewers. Third, CSRs can be redacted and important information could be masked and unavailable. For example, serious adverse event narratives could be redacted [20].

Repositories of clinical study reports:

To increase access to data from pharmaceutical companies, some repositories were created that include ClinicalStudyDataRequest.com (www.clinicalstudydatarequest.com) (CSDR) and the Yale University Open Data Access (http://yoda.yale.edu/). Through these platforms, researchers can request access to the protocol, the CSR, case report forms, statistical analysis plan and IPD of a given study. Academic funders and non-governmental organizations such as Cancer Research UK, the Medical Research Council, Bill & Melinda Gates Foundation, and the Wellcome Trust are now also using the CSDR platform to share their data. In addition to peer-reviewed journal articles, some funders such as the UK NIHR Health Technology Assessment Programme (https://www.journalslibrary.nihr.ac.uk/#/) also produce detailed monographs containing much more data on trial reports including all sensitivity and subgroup analyses along with information on open-access data-sharing agreements. Furthermore, trial

websites also give access to detailed information such as the CSR, statistical analysis plans etc.

All these new sources of data (i.e., trial registries, CSR repositories, etc.) represent a great opportunity because they provide access to clearly needed information related to the methods used (e.g., protocol, statistical analysis plan, annotated case report form) and the conduct and results of the trial (e.g., summary results posted on a trial registry, IPD, analysis-ready dataset, CSR). However, contrary to journal publications, which are available from well-structured electronic bibliographic databases, these new sources of information are only available through various channels that are still rapidly evolving over time as new initiatives emerge [24]. Information available for a single trial is usually scattered and not linked, so the identification of all data for a given trial is challenging. Using these data also raises specific issues related to the risk of double counting the same study [18] and possible discrepancies of the data reported in the various sources [25]. Solutions based on the concept of "threaded publications," whereby all the various reports and publications related to a trial are linked (published protocol, results paper, secondary commentaries, CSR, IPD, etc.) [26], are being explored [27]. Particularly, the OpenTrials database aims to host and match all existing trial publications and data in a user-friendly web interface to provide a comprehensive picture of all the data and documents available for a trial [28].

Methods for evidence synthesis must take into account these developments — for example, the search strategies must cover all these new sources of data [29] — and rules to manage discrepancies between different reports of the same trial must be pre-specified in the protocol. Furthermore, the process needs to be rethought because the large number of diverse sources needed to be continuously searched and the increased amount of data to be extracted is a huge amount of extremely time-consuming and burdensome work. Developing teams that are both

sufficiently large and have the necessary expertise to work with and analyse all these documents is becoming essential. Furthermore, to avoid a massive increase in the level of resources needed, we need to rethink the current ecosystem. This will be discussed in paper 3 of this series.

1.2. Better use of other types of data

New types of data are becoming available: IPD providing a deeper, new layer of the RCTs included in systematic reviews, and a new kind of data (routinely collected data), which have not been used for systematic reviews to a large extent.

1.2.1. Individual patient data

Meta-analyses mainly synthesize summary data from RCTs. However, IPD meta-analyses have important advantages [24]. With IPD meta-analysis, it is possible to verify the results [30], harmonize outcomes, use harmonized and appropriate analyses to avoid bias [31] and approach the question of precision medicine by assessing the treatment effect in subgroups of patients [32]. Also, there is some evidence that IPD meta-analyses can influence the design, conduct and analysis of subsequent trials [33]. Such meta-analyses can particularly affect the selection of participants, choice of comparator, and sample size calculation. In the past, IPD meta-analyses were limited because of important barriers to data availability. However, mentalities and practices have been changing, and several initiatives and policies to increase data-sharing have emerged [34–37].

Accordingly, access to IPD is increasing rapidly, and making use more often of these data would be an important step forward for systematic reviewers as well as decision-makers [38]. The International Committee of Medical Journal Editors (ICMJE) requires that manuscripts of clinical trials submitted to ICMJE journals as of July 2018 contain a data-sharing statement

and that clinical trials that begin enrolling participants on or after January 1, 2019 include a data-sharing plan in the trial's registration record [39,37]. Such initiatives are timely because research has shown that participants would agree to sharing their data for a wide range of uses, with less than 8% feeling that the potential negative consequences of data sharing outweigh the benefits [40].

However, despite these initiatives and an increasing endorsement of data sharing, meta-analyses of IPD can take longer and be more expensive than meta-analyses of aggregate data [41]. Access to and use of IPD remains difficult particularly because of the lack of permanency of trial staff (including retirement or death of the PI), lack of continued resources to prepare data sets or to anonymise data once funded study has finished, lack of standard operating procedures by some smaller institutions, fear that major data errors will be uncovered, or just apathy or possessive mentality. A study in orthopaedic surgery exploring the feasibility of IPD for 39 research questions including 273 RCTs, showed that only 13% of investigators agreed to share data; accordingly, data would only be accessible for 15% of participants of this set of trials [42]. A recent study showed that IPD was accessible for only half of the trials published in leading journals [43]. A systematic review of 760 published IPD meta-analyses showed that only 25% retrieved 100% of the eligible IPD and half retrieved less than 80% [44], with no evidence of improvement in the retrieval rate over time.

In addition, reanalysing IPD requires substantial resources and expertise. Contacting trialists (academic investigators or drug manufacturers), applying for access to IPD, negotiating confidentiality and data use agreements and contracts, technically gaining access to data and meta-data, understanding the structure of the database, querying possible data errors and undertaking analyses remains challenging and time-consuming, especially after funding for the main trial has ceased.

Moreover, IPD meta-analyses are not appropriate for all clinical questions. Indeed, an essential step in research is to determine the extent and scope of evidence synthesis required to ensure that the research efforts undertaken are consistent with the relevance of the clinical question. For example, for an emergent public health issue, a rapid review ─ i.e., a form of knowledge synthesis in which components of the systematic review process are simplified or omitted to produce information in a timely manner [45] ─ seems appropriate, whereas an IPD meta-analysis seems preferable for a clinical question for which we want to identify the characteristics of patients responding to treatment.

1.2.2. Large-scale routinely collected data

The primary research landscape is changing considerably with increasing access to large-scale health data routinely collected for administrative or clinical purposes. These data are defined as "data collected without specific *a priori* research questions developed prior to utilization for research" [46]. They include health administrative data, data warehouses of electronic medical records, primary care medical record data, and disease registries [47]. These large-scale routinely collected data represent a real opportunity to transform health research, conduct real-life clinical research and improve healthcare efficiency [48].

Overall, 85% of comparative effectiveness evidence is from non-experimental data [49]. There is evidence that only a small percentage of clinical guidelines are based on data from experimental studies. For example, a recent study showed that less than 20% of American Heart Association/American College of Cardiology recommendations are based on data from multiple RCTs (i.e., lower inherent risk for bias) and more than 45% are based solely on expert opinion [50]. Furthermore, the proportion of recommendations based on data from experimental studies (i.e., RCTs) has not increased over time [50]. According to some

experts, it is unrealistic to expect RCTs for every intervention and all combinations of these interventions in all patient subgroups [51]. Evidence is needed in a timely manner, and randomized trials take several years to design, pilot, deliver and report. Therefore, use of large-scale routinely collected data, especially in areas for which RCTs are rare or small, is an option that must be discussed [51]. Another example is the drug safety and effectiveness network (DSEN) which includes observational studies in network-meta-analyses of RCTs [52].

Nevertheless, use of this kind of data raises some issues related to the quality of the data, key missing data, the risk of confounding and misclassification bias. Approaching causality in such datasets can be difficult because of the observational nature of the data and risk of confounding biases. Furthermore, including such data is challenging particularly because of the large heterogeneity in the size and quality of datasets and methods used. However, with the increased interest, new concepts, methods, and tools are being developed to support use of these data for comparative effectiveness research [51]. For example, emulated trials aim to mimic a RCT when planning and conducting the analysis of routinely collected data or other observational data for comparative effectiveness research [53,54]. CERBOT (Comparative Effectiveness Research Based on Observational data to emulate a Target Trial; cerbot.org) is a new tool for helping researchers and clinicians articulate their research question in terms of a hypothetical RCT (the target trial) and analyse observational data accordingly [53]. Specific reporting guidelines for reporting these studies using routinely collected data are now available [46], and a specific tool for assessing risk of bias of non-randomized studies of interventions (ROBINS-I) is now available [55]. Such data cannot be ignored during the evidence synthesis process. However, we need to assess in a more comprehensive and systematic way the validity of data and explore appropriate methods for determining whether

and how these data should be included in systematic reviews and other forms of evidence synthesis [56].

2. Using new methods for evidence synthesis

The current evidence synthesis enterprise relies on multiple research teams all over the world independently deciding their question of interest and for most, working independently on evidence synthesis. These teams frequently address similar research questions, with no standard or structured approach planned for future updates. The system produces a wide range of disparate, redundant and outdated pairwise meta-analyses. It involves a considerable amount of resources but is not answering patients', care providers' and decision-makers' needs and is responsible for considerable research waste [57].

The Cochrane collaboration has aimed at some form of control on prioritising questions and avoiding overlap by encouraging groups to define relevant titles, plan for updates and use methods such as optimum information size. They proposed to periodically assess all Cochrane reviews to determine whether an update is needed considering a number of different factors synthesized in a decision framework [58].

Furthermore, new methods based on the concept of a "living" evidence synthesis enterprise opposed to a one-shot process have recently emerged.

2.1. Living systematic reviews

More than 20 years ago, the introduction of cumulative meta-analyses highlighted the importance of integrating new evidence as it became available [59]. Considering the large number of outdated systematic reviews and the difficulties in managing the updating process, some researchers proposed new methods — living systematic reviews [60] — representing high-quality, up-to-date evidence synthesis, updated several times per year to add all new

RCTs as soon as they are available [60,61]. Under the auspices of the Cochrane Collaboration, a living systematic review network launched February 2016 included Cochrane and non-Cochrane researchers, policymakers and guideline developers. Four living systematic reviews are now available in the Cochrane Library [62–65]. However, living systematic reviews and meta-analyses as of now focus on a narrow scope of evidence mostly based on pair-wise direct comparisons of two treatments.

2.2. Living network meta-analyses

To overcome the limitations of living systematic reviews, a paradigm shift has been proposed: to move from living systematic reviews toward a global live cumulative or living network meta-analysis (NMA) ─ i.e., technique for comparing interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies ─ considering all available interventions for a given condition and incorporating new evidence as soon as it is available [66,67]. Investing a massive amount of resources to produce an NMA and not maintaining it afterwards does not make sense. However, most end-users engaged in the funding or production of systematic reviews do not seem to view the importance of updating regularly systematic reviews and to consider a living process rather than a one-shot process. As an example, for a living NMA for second-line treatments of advanced non-small cell lung cancer, the workload of an update was estimated at 10% of the initial work in terms of number of records needing to be "screened" and number of trials to be extracted, considering the same pace of evidence generation over time [68,69].

A living NMA consists of 1) performing an initial NMA and 2) maintaining this NMA by an iteration of six methodological steps over time. These steps are 1) adaptive search for treatments and trials, 2) crowd-sourced screening of reports and selection of trials, 3) data extraction, 4) assessment of risk of bias, 5) updating the network of trials and synthesis, and

6) disseminating results [68]. To cover the whole evidence for all treatments (i.e., new evidence both for treatments already in the network of trials and also for novel treatments), an adaptive search strategy that incorporates additional keywords pertaining to the novel treatments over time needs to be implemented. This adaptive search strategy implies that the interventions of the PICO criteria need to be slightly different from those for classical systematic reviews, more inclusive (treatment category in addition to drug names) and evolve over time (including new drugs assessed). A living evidence synthesis community should be set up to identify the most relevant research questions and maintain the living cumulative NMAs over time. For a given topic, the living evidence synthesis community could consist of different embedded groups with different backgrounds and skills (e.g., people interested in the disease, including patients or their representatives, content experts, methodological experts). We describe the proposed methodology in Figure 1 and at http://www.livenetworkmetaanalysis.com.

The final output is an online living, comprehensive systematic review of all treatments and evidence synthesis (meta-analyses and NMAs) for multiple outcomes. The living NMA will be associated with a living sharing of data. Providing access to all extracted aggregated data allows for the self-correction of any error by the broader research community. It also allows end-users to perform additional analyses they consider relevant on the whole set or a subset of trial data. For example, living sharing of data may offer the possibility for different guideline developers to create their own evidence tables, thus increasing the uptake of evidence and potentially narrowing the gap between research publication and implementation.

The updating frequency is essential to ensure that the living NMA is both feasible and relevant according to the pace of evidence generation for the condition of interest. For some diseases, the pace of randomized evidence production is slow, and the iterations may occur at

longer regular intervals [69]. In other cases, therapeutic evaluation is moving rapidly, and iterations must occur after very short periods of time.

This new approach should be able to address the needs of the end users of comparative effectiveness reviews (Table 1). Indeed, living NMA provides a broad and up-to-date panorama of all treatments and trials available for a condition or a cluster of diseases under investigation. They can be intervention-focused to look for class effects as well as condition-focused. It is an ideal tool for medical decision-making because it also allows for inferences on treatment comparisons that have never been evaluated directly in a trial. A recent study showed that living NMAs provided strong evidence against the null hypothesis 4 years earlier than pairwise meta-analysis [70]. They also allow for identifying evidence gaps in a very powerful manner and guiding future primary research in areas for which evidence is most needed and therefore facilitate prioritizing the planning of future trials [71]. Specific models have been implemented to combine RCTs with observational studies to get a better sense of how the interventions behave in the "real world " [72].

Living evidence synthesis is probably not needed for all systematic reviews but become vital in case of a research question of very high importance, uncertainty with potential substantial health benefit or harm, or emerging evidence from trials in process. Likewise, living evidence syntheses are not open-ended and the question and process of their end must be planned (i.e., when it is unlikely that a new trial will change the results of the living NMA). Specific funds will have to be allocated for such living NMAs. For example, the Canadian government invested funds for the Drugs Safety and Effectiveness Network of the Canadian Institutes of Health Research.

2.3. Toward precision medicine

Medicine has evolved from the "one-size-fits-all" approach, a uniform approach believed to be valid for the whole set of patients, to a precision medicine approach in which healthcare is tailored to smaller strata/groups of patients, and possibly even to individual patients. Treatment effects vary according to multiple parameters, such as study location, type of intervention, and participant characteristics [73,74]. Therefore, the value for decision-making of a simple estimation of an average treatment effect across different settings, patient populations, and variations of an intervention in a meta-analysis is questionable. Hence, future evidence syntheses need to expand efforts toward a precision medicine approach. Increasing access to IPD through data sharing will favour a precision medicine approach at the meta-analysis level.

Reanalysing IPD offers the opportunity to examine specific subgroups of patients not previously considered. It should allow for more uniformly consistent and therefore more powerful analyses as well as better characterization of subgroups and outcomes as compared with meta-analyses based on aggregate data.

To achieve this stage of precision medicine, new techniques and statistical methods have been developed, for instance, to calibrate treatment effect estimates from a clinical trial to a target population [75]. The target population can differ from the study population in patient characteristics and/or medical practice due to temporal or regional differences [75]. New methods for treatment effect calibration based on the characteristics of the population have been developed and involve a combination of outcome regression methods, weighting methods based on a propensity score model and a conditional effect model [75]. Another example is predictive modelling with electronic health record data, which is anticipated to drive precision medicine and improve healthcare quality [76]. Deep learning methods with

these records can be used to create accurate and scalable predictions for a variety of clinical scenarios, including focusing on specific sub-populations [77].

This new approach is a very ambitious endeavor requiring significant expertise and resources that will allow a new framework of research activity that is both of high value to end users but also of professional and career advantage to researchers.

3. New approaches and tools to accelerate evidence synthesis

The rigorous methodology of systematic reviews (exhaustive search of trials, minimization of subjectivity by independent duplicate assessments, assessment of risk of bias within trials) is inherently resource-intensive, especially for a broad and comprehensive systematic review incorporating NMA. Updating systematic reviews is also time-consuming and burdensome. However, new approaches should help accelerate these processes. Particularly, automation technologies on the one hand and crowdsourcing on the other could enhance the feasibility and sustainability of the evidence synthesis enterprise and improve efficiency [78].

3.1. Automation technologies

For many repetitive and labour-intensive tasks of evidence synthesis, automation can and should be preferable and more sustainable [78]. New technologies such as textual analysis, semantic analysis, text mining and data linkage could have a major impact on the delay of systematic reviews (e.g., EPPI-reviewer [79]). Automated natural language processing (text mining) may help overcome resource-intensive manual screening [80–82], data extraction, assessment of risk of bias and reporting the findings of a systematic review [83–87]. Semi-automated web applications (AbstrackR [88], Rayyan [89], RobotAnalyst [90]), that employ machine-learning and text-mining technologies, are now available to support systematic reviewers during title and abstract screening. These systems use pattern recognition

algorithms to predict the likelihood of citations to be included or excluded for a given systematic review [82]. Such methods could save 30% to 78% of the workload but miss 4% to 5% of relevant studies [82,86].

In a living NMA, automatic screening using word embeddings can successfully be applied for updating NMA, diminishing the workload without missing any finally included citations [91]. Systematic Review Tool Box gives access to other relevant tools (http://systematicreviewtools.com/).

Nevertheless, current evidence processes remain very manual, and using all these tools in practice is still challenging. These automation technologies have been tested on only some specific clinical conditions, which raises concerns regarding their generalization in the practice of evidence synthesis. They have been mainly assessed in the selection phase of a systematic review, and further research and development are required for their transposition to other steps [78]. They have also been tested on traditional data sources (extracting data from PDFs of journal articles) rather than on new data sources such as structured registries. Finally, none of the combinations of these technologies has yet been tested.

3.2. Crowdsourcing

Partitioning of review tasks and subsequent online crowdsourcing could also facilitate and speed up some steps of the evidence synthesis process [92,93]. Cochrane Crowd is Cochrane's new citizen science platform applying crowdsourcing in the systematic review process. It offers the possibility to become a Cochrane citizen scientist by joining the collaborative volunteer effort to help categorize and summarize healthcare evidence and result in better healthcare decisions [94]. About 14,700 contributors from 189 countries have already performed about 3 and a half million classifications as of October 2019.

To reduce the workload on individuals involved in a living NMA, crowdsourcing could allow for distributing the tasks to a larger group of members of the living evidence synthesis community. Monitoring the development of novel treatments could also be opened up to a broad group of individuals actively engaged in the condition of interest. Records needing to be screened can be distributed across the group of experts and trials for extracting data across the group of trained reviewers, so independent selection and extraction in duplicate is guaranteed but the workload for each individual is minimized.

In a living evidence synthesis process, using crowdsourcing and crowdtiming — engaging people in corporate actions by giving their time rather than money to contribute to a project — may facilitate the commitment of volunteers and reviewers.

Conclusion

New sources and types of data and new methodological approaches and tools are now available to overcome the limitations of the current system of evidence synthesis, thereby allowing for rigorously conducted, up-to-date, living evidence syntheses that would be more useful for decision-makers. However, the implementation of these new approaches and methods requires considerable resources to support such an evolution and a substantial rethinking and redesign of the current evidence synthesis ecosystem, especially in terms of infrastructure. It implies conceptualizing evidence synthesis as a continuous process built around a clinical question of interest for patients and physicians and no longer as a small team independently answering a very specific clinical question at a single point in time. Furthermore, it requires better coordination in identifying and allocating research questions of interest among global actors.

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Table 1: Advantages of living network meta-analyses

Stakeholders	Advantages
Patients and physicians	• Answers the question of interest: "Which treatment works best?" • Gives access to a complete synthesis of all available evidence for all treatments over time collated in a freely accessible website • Saves time by avoiding the need to compile evidence from disparate, incomplete and potentially out-of-date systematic reviews, and overcomes issue of missing trials from these meta-analyses
Researchers	• Brings the communities of researchers and systematic reviewers together • Reduces waste in research by avoiding overlapping meta-analyses • Improves the identification of research gaps and prioritization of future trials • Gives access to a complete up-to-date synthesis required to justify a new randomized trial
Decision-makers	• Facilitates the production of trustworthy, up-to-date guidelines
Funders	• Facilitates the assessment of future research projects by providing a complete up-to-date synthesis

Figure 1: Living network meta-analysis to synthesize all available evidence for a given condition

Legend: At each update, the network of trials encompasses all treatments available for a given condition. Each node represents a treatment; an edge connects two nodes when at least one randomized trial has compared these two treatments. The node size is proportional to the total number of patients randomly allocated to the treatment and the edge width to the total number of trials between these two treatments. A research community interested in the condition will continuously update this evidence synthesis; different groups will perform specific steps of the process, as shown by the colour codes.

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