WHEN AND HOW TO UPDATE SYSTEMATIC REVIEWS

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A thesis submitted in fulfilment of the requirement for a PhD by Published Works

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List of Tables and Figures

Declaration

I, Alexander Tsertsvadze, declare that

(a) the submitted material as a whole is not substantially the same as published or unpublished material that I have previously submitted, or am currently submitting, for a degree, diploma, or similar qualification at any university or similar institution;

(b) that I have stated clearly which parts of the work or works submitted have previously been submitted for any such qualification; and

(c) where the work submitted includes work conducted in collaboration with others, I have provided a written statement on the extent of my individual contribution to the material and the conditions and circumstances under which the work was carried out. This statement has been signed by all collaborating parties.

Index of Published Works for Consideration

Publication #	Publication reference	Scopus citation index[μ]
1 (Appendix 1)	Moher D, Tsertsvadze A. Systematic Reviews: When is an Update an Update? *Lancet* 2006; 367: 881-883.[£]	54
2 (Appendix 2)	Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M, Barrowman N. A Systematic Review Identified Few Methods and Strategies Describing When and How to Update Systematic Reviews. *J Clin Epidemiol* 2007; 60: 1095-1104.	45
3 (Appendix 2)	Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M, Barrowman N. When and how to update systematic reviews. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: MR000023. DOI: 10.1002/14651858.MR000023.pub3.	52
4 (Appendix 3)	Garritty C, Tsertsvadze A, Tricco AC, Sampson M, Moher D. Updating Systematic Reviews: An International Survey. *PLoS ONE* 2010; 5(4): e9914.	24
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6 (Appendix 5)	Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S, Motala A, Tsouros S et al. A surveillance system to assess the need for updating systematic reviews. *Systematic Reviews* 2013; 2:104.	8

[μ] Last updated on 2 December, 2016

[£]This commentary is an important contribution to the field. The definition proposed here has been adopted by the Cochrane Collaboration and it is included in *Cochrane Handbook for Systematic Reviews of Interventions* [1]

Statement of Candidate's Contribution to Published work

Contributions of the candidate	First author's agreement
Publication 1. Systematic Reviews: When is an Update an Update? *Lancet* 2006; 367: 881-883.	D Moher "Alexander should very likely have been the first author. When we submitted the manuscript he was the first author. Somehow it got reversed on publication. I tried to change it when I noticed but the journal said it was too late."
Publication 2. A Systematic Review Identified Few Methods and Strategies Describing When and How to Update Systematic Reviews. *J Clin Epidemiol* 2007; 60: 1095-1104. **Publication 3.** When and how to update systematic reviews. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: MR000023. DOI: 10.1002/14651858.MR000023.pub3.	D Moher "I can confirm that Alexander played a very significant role in this systematic review."
Publication 4. Updating Systematic Reviews: An International Survey. *PLoS ONE* 2010; 5(4): e9914.	C Garritty "I can most certainly confirm that Alexander's contribution on the manuscript was substantive. He provided valuable input on the survey design, and protocol. In addition, he reviewed the analyses and assisted in the interpretation of the findings. His most significant contribution was in providing thorough input and edits on the

	drafted manuscript, and adding to the discussion section. In summary Alexander's contribution was significant and was the rationale for providing him with second authorship."
Publication 5. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. *J Clin Epidemiol* 2011; 64(11): 1208-1215.	First author
Publication 6. A surveillance system to assess the need for updating systematic reviews. *Systematic Reviews* 2013; 2:104.	N Ahmadzai "I do confirm Alexander's substantive contribution in this work with respect to different tasks; for instance, protocol, study selection/data extraction, analyses, interpretation, and write-up at the Ottawa Evidence-based Practice Center."

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality

CADTH: Canadian Agency for Drugs and Technologies in Health

CAG: Cochrane Airways Group

CER: Comparative Effectiveness Review

CMA: Cumulative Meta-Analysis

CMR: Cochrane Methodology Register

CPG: Clinical Practice Guideline

CRD: Centre for Reviews and Dissemination

CRG: Cochrane Review Groups

DERP: Drug Effectiveness Review Project

ECRI: Emergency Care Research Institute

EHC: Effective Health Care

EPC: Evidence-based Practice Centre

FDA: Food and Drug Administration

HTA: Health Technology Assessment

IPD: Individual Patient Data

KQ: Key Question

MA: Meta-Analysis

MHRA: Medicines and Healthcare Products Regulatory Agency

NA: Not Applicable

NICE: National Institute for Health and Care Excellence

NMA: network meta-analysis

OIS: Optimal Information Size

OR: Odds Ratio

PICO: Population, Intervention, Comparator, Outcome

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PUG: Panel for Updating Guidance

RCT: Randomised Controlled Trial

RoB: Risk of Bias

SR: Systematic Review

STL: Search Time Lapse

UK: United Kingdom

US: United States

VOI: Value of Information

Word count

Summary: 351 words

Main text (excluding tables, figures, and reference list): 11,500 words

Summary

Governments, funding agencies, academic institutions, and health care policy makers are increasingly investing in the design, development, and dissemination of systematic reviews (SRs) to inform clinical practice guidelines, ethical guidance of clinical research, and health care practice and policy. SRs need to be sensitive to the dynamic nature of new evidence, such as published papers. The emergence of new evidence over time may undermine the validity of conclusions and recommendations in any given SR and subsequent practice guideline. This issue has only started to be more seriously considered during the last decade or so. Now it is clear that the use of out-dated evidence can lead to a waste of resources, provision of redundant, ineffective or even harmful health care.

The author of this dissertation and his colleagues conducted and published three empirical studies and two conceptual articles (in six peer-reviewed journal publications), which addressed the methodologic aspects of when and how to update SRs. This PhD project provides a summary of these publications. The work described herein has had a significant impact on raising awareness and initiating new research efforts for keeping SRs up-to-date.

Publication 1 proposed the first formal definition of what constitutes an update of a SR. The article presented distinguishing features of an updated vs. not updated or a new review. Publication 2 (or Publication 3) systematically reviewed methods, techniques, and strategies describing when and how to update SRs (Study #1). Publication 4, an international survey (Study #2), identified and described updating practices and policies of organisations involved in the production and commission of SRs. Publication 5 reviewed the knowledge and efforts in updating SRs and provided guidance for authors and SR groups as to when and how to update comparative effectiveness reviews produced by the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centres (EPCs) throughout North America. Publication 6 (Study #3) described the development, piloting, and feasibility of a surveillance system to assess the need for updating comparative effectiveness reviews produced by the AHRQ's EPC Program. This surveillance

method has proved to be an efficient approach for prioritising SRs with respect to updating need.

1. Background

1.1. Systematic reviews: their role and importance

Professionals involved in the delivery of health care are faced with the challenge of how best to keep themselves up-to-date with advances in their speciality. Continuous professional education and quality improvement carried out in health care systems should be based on the totality of available up-to-date evidence [1-3]. An efficient use of reading time would be to review a single report that synthesizes the findings of many individual studies. Systematic reviews (SRs), alone or incorporated into clinical guidelines, fulfil this function.

A SR is an explicit form of evidence summary which addresses one or more clearly formulated questions for any given health problem by synthesising empirical results of relevant primary research studies [4]. Ideally, any SR should be based on a pre-defined transparent protocol aimed at minimizing or avoiding bias, which details a precise and clear evidence-based search methodology to identify and retrieve the global evidence, subjecting it to specific eligibility criteria, appraising, and summarizing the results of studies qualitatively or quantitatively [3, 5].

Over the past two decades, SRs have become integral building blocks and components of health technology assessments (HTAs) and clinical practice guidelines (CPGs). They help to fill in the gaps between empirical evidence and healthcare decisions. Therefore, governments, health policy makers, patients, and other stakeholders are increasingly involved in the commission, design, production, and/or use of findings from SRs to inform their decision-making process [6-9]. Besides, SRs help to identify gaps in evidence, highlight unmet needs, and prevent or minimise redundant research [10]. SRs may also inform ethical and methodological issues for designing future primary studies [11, 6]. SRs, HTAs, comparative effectiveness reviews (CERs), other types of evidence syntheses are conducted by either small teams of researchers or large organisations such as Cochrane (global network), the National Institute for Health and Care Excellence (NICE) in the UK, the Agency for Healthcare Research and Quality (AHRQ) in the US, and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada.

1.2. Keeping systematic reviews up-to-date

The value of SRs is maximised when they are up-to-date [12, 7, 13, 14]. As evidence base of health science is continually evolving with the emergence of new research, some health care interventions currently believed to be effective and safe may in future be shown to be ineffective or harmful or vice versa [7, 15, 16]. Moreover, evidence on new population subgroups, interventions (e.g., oral glycoprotein IIb/IIIa inhibitors), and health outcomes (e.g., quality of life scales) will emerge and modifications in dosing of interventions or improving surgical skills will take place over time [7, 17]. Ignoring these changes could undermine the validity of conclusions in SRs and CPGs, thereby compromising healthcare policy decisions. Lack of attention to updating any given evidence-base may lead to a waste of resources, redundant research, ineffective and sometimes harmful healthcare delivery [14]. Additional advantages of updating SRs may be to a) increase the precision around a pooled effect estimate [17], b) incorporate delayed publications or grey literature to minimise the effects of time lag bias or publication bias [18], c) correct errors or typographical errors in the published version, d) incorporate relevant evidence (original searches may have missed some relevant studies) [14], e) improve methodological and reporting quality of a review [19], and f) ensure overviews incorporate SRs that are up-to-date [20].

In light of the growing number of new primary studies, the issue of keeping SRs up-to-date becomes even more relevant, although challenging. For example, Bastian and colleagues showed that in 2007, there were 11 SRs and 75 trials published daily [21]. Similarly, Moher and colleagues identified 300 SRs indexed in Medline during November of 2004 with a corresponding estimated publication rate of 2,500 reviews per year [22]. A recent study [23] estimated that more than 8,000 SRs were indexed in Medline in 2014, corresponding to a 3-fold increase over the last decade in 2004. The empirical evidence on the consequences of updating SRs with respect to their content and conclusions has been conflicting. Some studies indicating important changes in conclusions and others showing no such changes in most of the updated SRs [24, 16, 25-28, 17, 29].

Shojania and colleagues defined several quantitative (e.g., change in statistical significance of the pooled estimate if a meta-analysis is updated with a new study)

and qualitative (e.g., a new harm, a new alternative therapy) signals indicating when any given SR needs to be updated ('the Ottawa method') [24]. The application of these signals to 100 SRs showed that the median time to either of these signals indicating the need for updating a SR after its publication was 5.5 years (95% CI: 4.6, 7.6). However, 23 of the SRs had signals indicating the need for updating within two years, 15 within one year, and seven at the time of publication. The odds of signals for updating were significantly higher for cardiovascular topics than for other topics [24]. A survey of 101 Cochrane childbirth reviews (issue 3, 2007) found a shorter updating interval, i.e., the median time to the first update to be 3.3 years (95% CI: 2.7, 3.8) with any quantitative changes in 71% of the reviews that included new studies [27]. Similarly, the study by Peterson and colleagues demonstrated a mean of 24.9 (standard error of 1.96) months to an update based on the analysis of 41 drug CERs that were commissioned by the Drug Effectiveness Review Project (DERP), a collaboration between US Medicaid agencies and the CADTH [30]. Higgins and colleagues surveyed 481 Cochrane reviews in the 1998 issue 4 of the Cochrane Library of which 65 had included at least one new study since their publication. The statistically significant pooled Peto's odds ratio (OR) was changed to non-significant for 26% and vice versa for 69% of the 65 updated reviews [26]. French and colleagues followed-up 362 Cochrane reviews from their original publication in 1998 to 2002 and found that 70% of them had been updated during the 4-year period. Only 9% of the updated reviews had a 'major change' ('changes that alter the substance or meaning of a section or alter the interpretation') in their conclusions [25]. Three other studies demonstrated similar findings, showing no major changes in the effect estimates of updated SRs [29, 28, 17].

1.3. Barriers to updating systematic reviews

The importance of the methodology for updating SRs has not been well recognised until the last decade. For example, the relative paucity of well-elaborated methods for updating SRs contrasts with substantial developments in other methodological areas such as imputation of variance, publication bias, or assessment of heterogeneity. Similarly, more work has been devoted to the development and evaluation of the methodology for updating CPGs than for SRs [7].

There has been little evidence or guidance which would indicate what proportion of SRs are in need of updating, when to initiate an update, and how best to implement it [14]. Organisation such as Cochrane have a policy of updating their SRs every two years [5]. Although Cochrane have invested substantial efforts in keeping SRs up-to-date, non-Cochrane SRs, which account for about 80% of all published reviews are not usually updated. Specifically, within 2 years of their publication, only 2.3% of SRs published in peer-reviewed journals had been updated compared to 37.6% of those published by Cochrane groups [22, 7]. Another study showed similar results with half of 36 Cochrane reviews (issue 2, 1995) updated compared to only one of 39 reviews published in paper-based journals and indexed in Medline in 1995 [31]. The update rates have been low even among Cochrane reviews. For example, in one empirical study of the 101 Cochrane pregnancy and childbirth reviews published in issue 3 of 2007, only 32.7% were updated within the 2-year period of its publication [27].

There have been multiple underlying barriers to a routine updating of SRs: a) absence of definition of what an update constitutes, b) lack or uncertainty as to when and how to update, b) high costs and lack of resources or funding, c) logistical issues, d) long period of time between the protocol formulation and review publication, e) original authors changing their affiliations, and f) original authors' loss of interest or lack of motivation [7, 14, 32-34]. In their study, Henderson and colleagues, identified 33 barriers to successful updating of a review [35].

Up until 2006, there was no formal definition of what constitutes an update of a SR. Without a definition, readers may encounter problems in determining if a SR had been updated or not. Also, researchers who surveyed updating practices across different groups or organisations may have perceived updating processes differently, leading to inconsistent assessments of currency of SRs. These differences, in turn, could have rendered these studies non-comparable [12].

Likewise, there has not been a standard methodology to assess the need for updating a review at a given point in time [7, 13, 29]. Periodic literature surveillance [36], obtaining expert opinion [37], and assessing the need for updating[38-40] help to prioritise SR updates which is a an efficient approach. In contrast, updating SRs at

arbitrarily defined time intervals is likely to result in inefficient use of resources, as reviews from diverse clinical areas have different need for updating depending on the pace of developments occurring in a given clinical area [7, 29]. For example, one study [30] has empirically shown that for drug CERs, the evolvement of evidence (i.e., emergence of new drugs, new safety alerts, and number of new trials) in psychiatric topics occurred at a faster pace compared to that in non-psychiatric topics such as endocrinology, respiratory, pain, or cardiology (mean number of new relevant citations: 38.4 vs. 8.2, p=0.012). The authors also identified that significant predictors for updating were the numbers of new relevant trials (OR=1.06, 95% CI: 1.03, 1.10) and new drugs (OR=5.71, 95% CI: 1.68, 19.44) [30].

1.4. Introduction to published work

In order to address the above-mentioned gaps and methodological challenges of updating SRs, the author of this dissertation and his colleagues conducted and published three methodological empirical studies (Publications 2, 3, 4, and 6) and two non-empirical conceptual works (Publications 1 and 5) presented in 6 peer-reviewed publications, which are included in this thesis (Appendices 1-5) [12, 7, 41, 13, 14, 38]. Publication 1 [12] proposed the first formal definition of what constitutes an update of a SR. The article presented distinguishing features of an updated vs. not updated or a new review. Publication 2 (or Publication 3; Study #1) [7, 41] is a SR of methods and strategies describing when and how to update SRs. Publication 4 (Study #2) [13], an international survey, identified and described updating practices and policies of organisations involved in the production and commission of SRs. Publication 5 [14], reviewed the knowledge and efforts in updating SRs and provided consensus-based guidance for authors and institutions conducting SRs as to when and how to update comparative effectiveness reviews (CERs) produced by the AHRQ's Evidence-based Practice Centers (EPCs) throughout North America [42]. Publication 6 (Study #3) [38] describes the development and piloting of a surveillance system (consisting of limited literature search, identification of qualitative and quantitative signals triggering updating, and expert opinion) to assess the need for updating CERs produced by the AHRQ's EPC Program [42].

2. What is an Update of a Systematic Review

Publication 1 (Appendix 1) – Systematic Reviews: When is an Update an Update? [12]

2.1. Introduction and rationale

In this publication, we proposed the first formal definition of what constitutes an update of a SR. We acknowledged that the lack of a formal definition for updating would lead to inconsistent conceptualization of what an update of a SR is or whether or not any given review has been updated. Moreover, researchers surveying updating practices across relevant agencies or examining overviews reporting on updating status of included SRs could perceive and qualify these processes differently, thereby rendering the current and future research studies non-comparable.

2.2. Definition of an update of systematic review

We believe that the introduction of a formal definition and explanation for updating a SR is long overdue. The definition of "to update" means "to extend up to the present time" or "to include the latest information". We defined an update of a SR as a discrete event with the aim to search for and identify new evidence to incorporate into a previously completed SR.

The central and necessary element of an update is the effort to identify new evidence. The term "new evidence" in this context is used broadly—evidence that has not been included in the previously completed review. For example, the authors consider updating takes place when a search strategy of the original review is applied to an additional (not searched previously) database to identify any evidence not previously incorporated. Alternatively, updating could be initiated after a specific period of time has elapsed since the completion of the original SR, which allows for the identification of new evidence that has emerged during this time. We note that even if a search does not identify any new relevant evidence, this event still constitutes an update. In other words, to undertake an updating process, a systematic search needs to be initiated with the purpose of determining whether or not new evidence exists.

In an update, the most of the originally formulated protocol (e.g., eligibility criteria, search strategy) is retained, or some parts of it are extended to accommodate newly identified evidence (e.g., new subpopulation, new type of treatment or outcome). We do not consider an update a re-analysis or replication of the original SR using a new or modified method (e.g., statistical pooling, risk of bias tool) without initiating a new search. The use of a new search terminology without an effort to identify new evidence would not be regarded an update either. Corrections of mistakes, errors, or typographic errors detected in a previously completed SR would not constitute an update, since these operations do not allow the identification of any new evidence.

2.3. Key messages and significance of Publication 1

The consistent definition, conceptualisation, and use of updating context across research community is an important step towards international harmonisation of updating SRs.

This paper is published in *the Lancet*. *The Lancet* is one of the highest impact factor biomedical journals across the globe (45.217). It belongs to the General and Internal Medicine category. In this category which includes a total of 154 journals, *the Lancet* ranks as the 2nd (Q1 quartile).

A high number of citations for this publication (Scopus index: 54; on 2nd December, 2016) is indicative of a high uptake and wide use of the definition by the international scientific community. The definition proposed in this publication has been adopted and used by Cochrane and is included in the Cochrane Handbook for Systematic Reviews of Interventions [5]. Moreover, the paper has been cited by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The journals citing this publication cover a wide number of different subject areas such as general medicine (*Ann Intern Med, Nature Medicine, BMJ, PLoS ONE, PLoS Medicine*), specialist clinical (*Br J Psychiatry, Hypertension, Blood Press*), methodology (*Stat Methods Med Res, J Clin Epidemiol, Syst Rev, Biom J*), alternative/complementary medicine (*J Altern Complement Med, Phys Ther*), nursing (*Nursing Outlook*), and public health (*Health Policy*).

3. When and How to Update Systematic Reviews

Publication 2 (Appendix 2) - A Systematic Review Identified Few Methods and Strategies Describing When and How to Update Systematic Reviews [7]

Publication 3 (Appendix 2) - When and How to Update Systematic Reviews [41]

Information below is presented according to Publication 2.

3.1. Introduction and study rationale

Although updating SRs may yield important additional information, this process can be as costly and time consuming as conducting a new review. The decision when to update a SR depends on several factors: a) rapidity and scope of scientific developments, b) nature of the health condition, and c) public health importance of the health condition. We conducted a SR of strategies and methodologies describing when and how to update SRs. The aim was to identify, synthesise, and characterise these approaches in terms of their strengths, limitations, and applicability.

3.2. Methods

We searched Medline (1966 to December 2005), PsycINFO (1955 to June, Week 1, 2005), and the Cochrane Methodology Register (CMR) (Cochrane Library Issue 1, 2006). The reference lists of potentially relevant reports were scanned. The proceedings of the 13th Cochrane Colloquium (August 2005) were also hand-searched. The searches were not restricted by language, publication type, or study design. Three investigators independently screened titles, abstracts, and full-text reports of all the retrieved bibliographic records. I and another reviewer independently extracted relevant data using a pre-piloted 15-item extraction form. Disagreements at the screening and extraction phases were resolved by discussions.

Included approaches for updating SRs were grouped as strategies, techniques, and statistical methods. The strengths and limitations for each approach were determined through a consensus-based judgment reached by the review authors. The approaches

were described in terms of when and how to update, comprehensiveness (e.g., covering clinical, statistical, or other domains), strengths, and limitations.

3.3. Results

Fifteen publications (four strategies, one technique, and two statistical methods) describing when and/or how to update SRs were included in the review **(Table 1)** [7].

Strategies and techniques for updating SRs

The first strategy (Steps in maintaining an updated review) describes the process of maintaining updated SRs of randomised controlled trials (RCTs) evaluating the effects of perinatal care.

The second - Cochrane strategy (Maintaining an updated review) is based on the two-year recommended interval for an update to occur after the publication or completion of the review. If a review is updated less frequently than once in two years, the Cochrane requires that reviewers provide a commentary explaining the reasons why.

The third strategy (Assessment of need to update) proposed by the Cochrane Infectious Disease Group involves two steps and follows the two-year cycle updating policy. The first step is to assess whether a review is up to date by considering its age, availability of new relevant trials, and the number of participants in the new trials. The second step is to assess the importance of the topic through ascertaining the burden of disease and pace of development of the field. Both steps involve judgment decisions reached by an editorial consensus. This strategy assists in assigning an order of priority to reviews in need of updating.

The fourth strategy provides a guidance as to when and how to update SR or HTA. When conducting an update, the strategy suggests considering clinical endpoints, treatment characteristics, statistical methodology, public health impact of treatments, and the availability of resources.

Techniques for updating SRs

It is important that database searches performed for updating SRs retrieve all relevant records. Bergerhoff suggested that reviewers use the ‘‘entry date’’ field rather than the publication year when performing updating searches for SRs. This search results in a more complete retrieval of relevant records including those that have become available since the date of the last search.

Table 1. Strategies, techniques, and statistical methods for updating systematic reviews

Strategy or technique (author year; reference #) country	Domains covered[a]	Strengths	Limitations
Steps in maintaining an updated review (Chalmers 1993; #14[b]) The UK	Search strategy, administrative issues	a) Minimizes publication bias by obtaining grey literature and contacting authors for further information, clarifications	a) Inefficient, b) cumbersome to implement
Maintaining an updated review (Cochrane Handbook for systematic reviews of interventions 2005; #15) International	Search strategy, administrative issues, clinical, updating format	a) Periodic updating ensures validity at some time, b) timing is known (e.g., every two years)	a) Inefficient, b) two-year updating cycle may lead to outdatedness in rapidly developing fields or wasted resources in slowly developing fields
Assessment of need to update (Lutje 2005; #17) The UK	Search strategy, administrative issues, clinical, public health	a) Assesses the need to update, b) prioritises reviews requiring updating, c) efficient d) evidence-based editorial consensus on whether or not to update, e) algorithm of administrative actions	a) Unclear how to determine whether a review is out of date, b) unclear how to determine the importance of the topic in order to reach editorial consensus
Strategies for updating a review (Weller 1998; #18) Australia	Clinical, public health, economic, updating format	a) Applicable to systematic reviews, CPGs, and health technology assessments	a) General description of actions, b) low practical utility
Searching using the ‘‘entry date’’ field (Bergerhoff 2004; #19) Germany	Search strategy	a) Compensates for indexing lag by retrieving records indexed since the last search regardless of publication date	a) It may not retrieve non-English records or those without abstracts
Statistical method (author year, reference #) country		**Strengths**	**Limitations**
Identifying ‘‘null’’ meta-analyses that are ripe for updating (Barrowman 2003; #20) Canada		a) Relatively efficient, b) easy to use/compute formula, c) reduced type I error relative to conventional CMA, d) test sensitivity/specificity easily modifiable	a) Applicability limited to statistically non-significant MA, b) assumes no secular trend in effect and that the variance of pooled estimate shrinks at a rate inversely proportional to the total number of participants in all studies, c) test results are sensitive to studies’ sizes

Conventional CMA (Lau 1992, Lau 1995, Baum 1981, Berkey 1996; #21,#22,#23,#24) The USA	a) Defines the earliest time at which an intervention can be shown to be efficacious, non-inferior, or harmful, b) monitors the effect size and direction over time, c) timing for each update is known, d) ascertains the contribution of individual studies to the cumulatively pooled effect estimate, e) allows one to explore heterogeneity and perform sensitivity analysis, f) provides up-to-date information, g) useful in stopping ongoing trials or planning future trials	a) Inefficient if an update is conducted every time a new study becomes available, b) inflated type I error due to multiple testing, c) affected by publication bias
CMA using the cumulative slope as an indicator of stability; CMA for sufficiency and stability (Mullen 2001; #25) The USA	a)-g) of 'conventional CMA,' h) explores the stability of the effect size and informs the need for updating	a)-c) of 'Conventional CMA,' d) judging extent of stability is arbitrary, e) variance of the 'cumulative slope is invalid, f) minimum size of a meta-analytic database for fitting a regression line whose slope would be a valid indicator of (in)stability of effect not specified
CMA using sequential monitoring boundaries (Pogue 1997; #26) Canada	a)-g) of 'Conventional CMA,' h) controls type I error by using sequential monitoring boundaries	a)-c) of 'Conventional CMA,' d) requires prior calculation of the OIS, e) does not account for heterogeneity or bias among studies
Recursive CMA (Ioannidis 1999, Ioannidis 2001; #11,#27) The USA	a)-g) of 'Conventional CMA,' h) incorporates results from unpublished studies and follow-up or more detailed data for studies already included in the CMA, i) documents the evolution of results as missing, updated, and new data are incorporated in information steps, j) evaluates updated follow-up information, publication bias or lag, and heterogeneity, k) treatment effect estimates are based on relatively accurate and complete data	a) and b) of 'Conventional CMA,' c) unpublished and updated information must be carefully studied and verified to minimize bias, d) analysis of updated follow-up data may sometimes be inappropriate because many post-study patients will cross over, e) more costly and resource consuming than conventional CMA
MA=meta-analysis; CMA=cumulative meta-analysis; OIS=optimal information size; CPGs=clinical practice guideline(s)		

[a] Domains: search strategy, statistical method/technique, clinical (expert opinion, long/short–term outcomes, intervention, pace of development in the field, nature of condition), public health importance (severity of condition and prevalence), economical (e.g., resource availability), updating format (preference for electronic vs. paper-based format; information steps), and administrative issues (e.g., those related to the implementation of updating process of systematic reviews).

[b] Reference #s refer to those in the original publication (Publication 2, Appendix 2)

Statistical methods for updating SRs

Barrowman and colleagues [43] proposed a diagnostic test, which helps to assess if an additional new evidence may have been accrued which would be sufficient to turn a statistically non-significant result of a meta-analysis (MA) into a significant one, thereby rendering it in need of updating. Computer simulations indicated that the diagnostic test identified whether a MA was out of date with a sensitivity between 49% and 62% and a specificity between 80% and 90%, depending on the configuration of the simulation. This method predicts the appropriate timing for an update, requiring the conduct of search, screening, and only partial data extraction (e.g., number of additional participants), rather than spending considerable resources. The application of this method is limited to MA with a statistically non-significant result under the assumption that this may have been due to insufficient power.

The cumulative meta-analysis (CMA) [44] is a statistical procedure in which the combined effect estimate is sequentially updated by incorporating results from each newly available study. It documents trends in a treatment effect over time and provides clinicians and policy makers with up-to-date information. When done prospectively, CMA may identify the earliest time at which there is sufficient statistical evidence that an intervention is non-inferior, efficacious, or harmful, thereby serving as a signal to stop trials that are under way earlier than planned (or at least not to initiate any new ones) because of ethical concerns and economic implications. The use of CMA is a costly and cumbersome process, which is prone to lead to an inflated type I error rate due to repeated hypothesis testing. This limitation necessitates the adjustment of the alpha level of statistical significance [45]. For application to updating MA, CMA use has three extensions: a) cumulative slope as an indicator of stability (CMA for sufficiency and stability) [46], b) sequential monitoring boundaries [47], and c) recursive CMA [48].

3.4. Key messages and significance of Publication 2 (or Publication 3)

Because health care evidence continually evolves as new research becomes available, SRs need to be kept up-to-date. Ignoring new information may undermine the validity of not only SRs but also CPGs. Up to now, methods used for updating SRs in health care have not been systematically reviewed.

In general, the identified strategies and one technique do not include quantitative techniques, are arbitrary in nature, may be inefficient, are limited in applicability, and are not sufficiently comprehensive in terms of domains addressed. The effectiveness of these approaches is unclear because they have not been empirically tested or compared to one another. CMA and its methodological extensions are resource-consuming approaches for updating SRs. Although the method by Barrowman is less resource-intensive than CMA, it is strictly a statistical approach with limited application to only MA with statistically nonsignificant results.

The relative paucity of well-elaborated methods for updating SRs contrasts with developments in methods for updating CPGs as well as other methodological areas of conducting SRs (e.g., publication bias, heterogeneity). The findings of this review suggest that the importance of updating SRs has not been well recognized, and that considerably more investment should be made to investigate this construct. The development of adequate and cost-effective methodologies for updating SRs would be an important step toward maintaining SRs up to date. Additional efficiency may be gained with international harmonization of aspects of the updating process.

The author of this commentary intends on updating this SR to reflect methodological developments that have taken place in the past decade since the publication of this review. The updated review is expected to identify new checklists, statistical tools, multi-dimensional methods as well as economic decision tools guiding the updating process of SRs. Moreover, newly accrued empirical evidence on the longevity of SRs (until their conclusions are still valid) will inform the most optimal time when to update any given review. Ideally, the scope of this update should extend to unpublished methods for updating SRs as well as methods for updating CPGs.

This paper (Publication 2) is published in the *Journal of Clinical Epidemiology*. This journal is one of a higher impact factor biomedical methods journals (3.417). It belongs to two categories: 1) Health Care Sciences and Services and 2) Public, Environmental, and Occupational Health. In the first category, which includes a total of 88 journals, the *Journal of Clinical Epidemiology* ranks as the 10^{th} (Q1 quartile). In the second category (165 journals), this rank is the 22^{nd} (Q1 quartile).

This article has been cited 45 times since its publication in 2007 (in Scopus; 2nd December, 2016). The citing sources are the Cochrane Handbook for Systematic Reviews of Interventions [5] and multiple journals covering a wide array of subject areas such as general medicine (*Ann Intern Med, BMJ, PLoS ONE, J Evid Based Med*), specialist clinical (*Eur J Orthod, Kidney Int, BMC Pediatrics, J Pain Symptom Manage, Psychiatr Serv*), methodology (*J Clin Epidemiol*), and education (*Med Teach, Patient Educ Couns*).

The same study was also published by Cochrane (Publication 3)[41] and since its publication in 2008, it has been cited 52 times (in Scopus; 2nd December, 2016).

4. Updating Practices and Policies: International Perspective

Publication 4 (Appendix 3) - Updating Systematic Reviews: An International Survey [13]

4.1. Introduction and study rationale

It is not clear what are the updating policies and practices of organisations that commission or produce SRs. We conducted an international survey to describe the updating policies and procedures used by healthcare organisations producing and/or sponsoring SRs worldwide.

4.2. Methods

The survey consisted of 48 questions (including skip-logic functionality) covering the following topics: a) updating policies, b) responsibility for updating, c) changes in estimates of outdated reviews, d) updating approaches (e.g., when/how to update, surveillance, and triggers impacting updating decisions), e) barriers and facilitators to the updating process, f) views on harmonization of updating, and g) descriptive characteristics of the organisation and the representative key informant. The survey was provided to participants via the Survey Monkey web-based service (www.surveymonkey.com). The main survey was administered between 12 April and 8 June, 2007 with reminders emailed at one, three, and six weeks from the first point of contact.

A purposeful non-random sampling approach was used to sample organisations involved in undertaking or funding SRs. The sample was expended by including entities dealing with HTAs and CPGs. In addition, 52 Cochrane Review Groups (CRGs) were invited to participate in the survey. The final sampling frame consisted of 195 different organisations. Closed-ended questions were analysed using a descriptive summary of findings in the form of frequencies and percentages. A subgroup analysis was performed comparing Cochrane groups to non-Cochrane organisations for their responses across select updating characteristics. Survey findings were analysed using descriptive statistics.

4.3. Results

The initial survey response rate was 65% (127/195), of whom 10% (13/127) declined participation, leaving 58% of responders (114/195) who completed the survey. Thirty percent of all organisations (34/114) were CRGs. The 114 participating organisations were from 26 countries with the UK, the US, Canada, and Australia accounting for 62% (71/114) of the sample. About 70% (75/107) of the organisations were producers of SRs, 5% (5/107) were funders only, and 25% (27/107) were both funders and producers. Ninety-six percent (96/100) of the responders were not-for-profit agencies, with 40% of them being academic institutions and 21% National Government agencies. Eighty-five percent of funding was accounted for by Government research or infrastructure grants. While 20% (23/114) of the organisations reported to have been involved in the production or commission of SRs only, only 46% (52/114) of them reported a wider range of involvement including SRs, HTAs, and CPGs.

Approximately 96% (103/107) of the respondents agreed ‘strongly’ or ‘somewhat’ with our definition of updating [12]. About 80% of the organisations (84/107) viewed the importance of updating SRs as ‘high’ or ‘very high’. Of the respondent organisations, 57% (60/106) indicated having an updating policy, of whom only 29% (35/106) made reference to a written policy (29 of the 35 were CRGs).

About one-third of all respondent organisations (35/105) reported regular, whereas 59% (62/105) reported irregular updating practices. Approximately, 8% (8/105) of the organisations had not reportedly engaged in updating practices. Sixty-three percent (66/105) of the organisations reported to have conducted regular literature searches to identify new evidence, while 28% (29/105) reported no such activity. The most frequently used approach for updating SRs was based on a pre-set time frequency (66/99; 67%).

About half of the organisations (53/103) deemed that over 50% of their SRs were out-of-date. Authors of the original SRs (42/106; 40%) were most often considered responsible for ensuring the currency of SRs. About 16% of respondents thought that responsibility for updating was a collective effort shared among review authors, funders, information specialists, and policy-makers. The most influential predictors

for updating were formal request from a policy/healthcare decision maker (80/99; 81%), number of new studies identified (77/100; 77%), totality of all new evidence including benefits and harms (75/99; 76%), and emergence of new serious adverse event (74/100; 74%). Barriers to updating included resource constraints and limited funding (72/100; 72%), reviewer motivation (53/96; 55%), limited academic credit (49/100; 49%), and limited publishing formats (35/100; 35%). The majority of the respondents (70/100; 70%) indicated some support for centralised updating efforts across institutions or agencies that produce SRs. The most commonly perceived benefits of international harmonization efforts for updating were a more efficient use of existing resources (79/101; 78%) and access to new information, ideas, materials or other resources (79/101; 78%).

There were significant differences between CRGs and non-Cochrane organisations across certain updating characteristics: more CRGs than non-CRGs described their general updating practices as regular (31.8%, 95% CI: 11.40, 48.9), viewed authors as most responsible for updating (59.6%, 95% CI: 39.1, 72.1), and conducted regular literature searches to monitor the literature (23.5%, 95% CI: 4.3, 38.6).

4.4. Key messages and significance of Publication 4

We believe that this was the first survey to examine updating practices of organisations engaged in knowledge synthesis. It was guided by a conceptual framework, had a good response rate, and included strong international representation.

This survey revealed inconsistencies between the belief of the importance of updating and the limited updating activity among respondents outside Cochrane (nearly 70% of the respondents). Analysis of CRGs and non-Cochrane organisations showed several significant differences in approaches to updating. Most fundamental is the Cochrane's policy recommending the 2-year interval for an update (after publication or last update) and authors' agreement to keep reviews up-to-date. Not surprisingly, the CRGs perform updates in greater numbers than other respondent organisations. Within Cochrane, responsibility for updating resides predominantly with the authors. This did yield an advantage in that CRGs were able to draw on the same review team for updating to a greater extent than non-Cochrane respondents.

Still, when reviewers had responsibility for updating, reviewer motivation was the most prominent barrier to updating.

Placing the duty for updating mainly on authors of SRs has had some success within Cochrane although this may not be a practical approach for agencies that do not share its values and culture. Journal publishers and academic organisations can contribute to overcoming some of the known motivational challenges faced by authors with updating duties. Academic institutions can support updating by according academic recognition on par with conducting and publishing original reviews. Journals can increase publishing outlets for updates, for instance, when accepting a review for publication, by also committing to publishing any future updates. Organizations can make updates more prominent by tying them to the original review.

This survey was of descriptive nature, more appropriate for generating rather than testing a specific hypothesis. Some of the main limitations of this survey were its non-random sampling frame and the low participation rate (58%). Selection bias may have been introduced if participants (i.e., responders) of this survey were systematically different from non-participants in their characteristics that were associated with their responses.

This paper is published in the *PLoS One*. This journal's impact factor is 3.234. It belongs to the Multidisciplinary Sciences category, which includes a total of 57 journals. *PLoS One* ranks as the 9th in this category (Q1 quartile).

This article has been cited 24 times since its publication in 2010 (in Scopus; 2nd December, 2016). The citing sources are multiple journals covering a wide array of subject areas such as general medicine (*J Comp Eff Res, Science, BMJ, PLoS ONE*), specialist clinical (*Genet Med, Eur J Orthod, BMC Dermatol, BMC Pulm Med),* and methodology (*J Clin Epidemiol, Med Decis Making*).

5. Guidelines for Updating Comparative Effectiveness Reviews

Publication 5 (Appendix 4) - Updating Comparative Effectiveness Reviews: Current Efforts in AHRQ's Effective Health Care Program [14]

5.1. Introduction and rationale

To maintain relevance, SRs need to be updated as new evidence is produced [15, 16]. The lack of attention to updating may lead to evidence-based conclusions becoming outdated and sometimes misleading, thus compromising health care and policy decisions. These problems could lead to a waste of resources, provision of redundant or ineffective health care, failure to implement more effective health care, and possibly cause harm. Disseminating the updated reviews will increase the awareness of new findings among relevant stakeholders and the likelihood that new evidence is incorporated into clinical practice.

The AHRQ, like other large organisations producing evidence synthesis reports (e.g., Cochrane, NICE, CADTH), have faced a dilemma in relation to keeping their evidence synthesis research up-to-date. An important cornerstone of AHRQ's research is the Effective Health Care (EHC) program of which one of its mandates is to produce Comparative Effectiveness Reviews (CERs). A CER is a type of SR that synthesizes the available scientific evidence on a specific topic, beyond the effectiveness of a single intervention, by comparing the relative benefits and harms among a range of available health interventions for a given condition [42]. In this article, we report the current efforts and consensus-based guidance on updating SRs as applied to CERs.

5.2. When to update comparative effectiveness reviews

There has been a lack of knowledge and methodological uncertainty as to when any given SR needs to be updated [7]. Certain signals may trigger an update of a CER at any given time (e.g., results from newly published studies, newly emerged interventions or outcomes, devices, diagnostic tests). The optimal timing for updating a CER depends on the rapidity of scientific developments in a given clinical area as well as the nature and public health importance of the health

condition in question. Conducting periodic literature surveillance[36], obtaining expert opinion[49, 50, 37], with the application of quantitative and qualitative signals indicating the need for updating [24] are helpful sources for efficiently determining when to update a SR. Although surveillance search strategies typically are not comprehensive, they are useful in flagging CERs in need of updating. For example, Sampson and her colleagues [36] compared the performance of five different surveillance search techniques (i.e., related articles, clinical queries, CENTRAL, core clinical journals, and citing article) for identifying relevant new evidence needed for updating 77 SRs. The combination of the PubMed-related articles search and subject searching with clinical queries was the most effective approach.

Identifying new evidence on harms warrants at least the same rigor in surveillance search as that for benefits; it should be an integral part of the updating process. Drug warnings often based on adverse events data reported by consumers or medical providers can be found in nationally licensed databases (e.g., US Food and Drug Administration/FDA). Since such data are not routinely submitted for journal publication, it is recommended that during an update, peer-reviewed literature searches be supplemented by searches of specific repository sources of adverse events (e.g., the US FDA's Safety Information and Adverse Event Reporting System, the UK's Medicines and Health Care Products Regulatory Agency, Health Canada) [51].

Experts in the field are often aware of new developments before they become public (e.g., new drugs or devices, ongoing trials, articles in press, safety alerts). Expert opinion has been used in updating clinical practice guidelines [49, 50]. While reviewers are updating a CER, they may find expert opinion useful as a supplemental source for new evidence [52]. The experts may be asked of their opinion if the conclusion of any given review is still valid and whether or not they are aware of any new evidence that may change this conclusion [37].

Shojania and colleagues [24] proposed quantitative and qualitative signals indicating when a SR needs an update (the Ottawa method). They defined a quantitative signal as a change in the statistical significance for an effect estimate (at α=0.05) or a

relative change of ≥50% in the magnitude of an effect. The authors defined a qualitative signal as a qualitatively different characterization of effectiveness that influences clinical decision making (e.g., a new harm, a new alternative therapy, or a treatment expanded to a new patient subgroup).

5.3. How to update comparative effectiveness reviews

If new studies are published, new harms have emerged, or a new and more effective intervention(s) is introduced, the question of 'when to update' becomes 'how to update'.

Scope of updating considering key research questions and PICO framework

The updating process can be viewed as a continuum over a wide range of activities from a single update search (e.g., yielding no new evidence) to a comprehensive search leading to the incorporation of new evidence. Therefore, the rational choice of the scope for an update search will depend largely on where a given investigator stands along the continuum of updating process and available resources allocated to updating. The assessment process of the updating scope and corresponding modifications are depicted in **Table 2**.

Because medical disciplines are constantly evolving through emergence of new evidence, it is recommended that reviewers assess all key questions (KQs) of the original CER at the initial stage of updating. Specifically, they should determine the extent to which the constituent elements of the key research question(s) denoting Population, Intervention, Comparator, and Outcome (PICO) may have changed. If an update search does not identify any relevant evidence, the CER will not be modified. However, the status of the CER will be labelled as 'updated' by including information on the search dates and time periods covered by the search. When newly identified evidence does not entail the modification of any PICO elements of a KQ (e.g., no new population, intervention, or outcome identified), the update process will consist of only incorporating this evidence into relevant sections of the report (e.g., Results and Conclusion).

Table 2. Scope of updating and corresponding actions

Newly identified evidence	Action for updating a CER
Search performed but no new studies identified	• No action • Mark as 'updated' • Provide search sources, dates, period
Search performed and new studies identified (without identification of a new PICO element)	• Update Results and/or Conclusion sections • Mark as 'updated' • Provide search sources, dates, period
New evidence from already included studies (without identification of a new PICO element)	• Update Results and/or Conclusion sections • Mark as 'updated' • Provide search sources, dates, period
Search performed, new study or studies with one or more new PICO element identified: • New (sub)population(s) • New intervention(s) • New comparator(s) • New outcome(s)	• Extend the inclusion/exclusion criteria for corresponding PICO element to accommodate the incorporation of new evidence • Update Introduction, Methods, Results, and Conclusion sections • Mark as 'updated' • Provide search sources, dates, period
KQ=key question; PICO=population, intervention, comparator, outcome; CER=comparative effectiveness review	

However, if newly identified evidence includes a new PICO element (e.g., new harm and/or new subpopulation was identified), the eligibility criteria has to extend and the KQ be modified with respect to the given PICO element to accommodate this evidence in relevant sections of the updated CER (e.g., Introduction, Methods, Results, and Conclusion). The identification of evidence on the same intervention, comparator, and outcome as specified in a KQ of the original CER, but for people with a newly identified health condition, would not be an update of the previous CER because it entails the exploration of a new KQ.

Evolution of methods when conducting an update

Methods used to conduct CERs (e.g., methods for pooling, assessing the risk of bias, and grading the strength of evidence) continue to evolve over time. If some of these methods have changed by the time of an update, we recommend that investigators compare the methods used in the original CER with the newly developed methods. If the new methodology is an obvious improvement over the older one, the CER team should ideally re-review (e.g., appraise and grade) all previously and newly included studies using the new methodology for sake of consistency between the original and updated review. Moreover, critical feedback obtained on the original review can provide useful information regarding correct choices for the analyses the reviewers might consider conducting in an updated CER. For example, if a CER is criticized

for its use of a fixed-effect over random-effects model for pooling results of individual studies, conducting a sensitivity analysis using both pooling methods (or only random-effects model, if deemed appropriate) in the update might be reasonable.

Incorporating new evidence and reporting an update

To make updates most useful, reviewers need to describe the purpose and methods used for the update. Reviewers should explicitly note any changes in the scope, methods, and results for each KQ in the updated versus original review. The rationale for introducing any new methodology or different conceptual framework in the updated report also needs to be described.

Important elements to focus on include the search strategy, the yield of the searches, important characteristics of new evidence (number, type, size, and quality of studies; study participants; and outcomes), and main results, including how the conclusions of the update differ from those of the original review. When incorporating evidence on a new intervention, outcome, or subpopulation group, we suggest adding a new section in the Results chapter of the CER report.

The updating process will have optimal credibility if it is conducted and reported transparently. To ensure continued transparency, the EHC program should publish the titles of CERs selected for updating. Updated CERs should include a description of how they were updated. There should be adequate opportunity provided for public comment on both the CERs chosen for updating and subsequent updated draft reports. Posting a list of KQs for CERs that will be updated will ensure that a broad range of stakeholders have the opportunity to provide relevant new evidence that the project team might consider as informative to the decision-making process.

Issues of authorship and challenges of updating CER

Ideally, the original CER authors should be asked to conduct an update. But this approach may problematic because authors may be working on new topics, may have changed institutions or affiliations, or may not be interested in updating the already published CER. According to Garritty and colleagues [13], only half of the surveyed organisations involved in evidence synthesis were able to draw on the same

authors of the original review for updating. This phenomenon poses significant problems for the cost, time, and practicality of an update. Naturally, new reviewers would require additional time to become familiar with a CER. In addition, knowledge of project history would be diminished or perhaps lost, and issues of replication and transparency could arise if the original CER was not well reported. These factors combined would add to costs and jeopardize the feasibility of updating.

If an update involves new authors, it is important to discuss the author issues as early in the updating process as possible. One objective would be to ascertain the level of involvement and authorship of the original CER team in the update. These discussions can be informed by examining current international policies and guidance on authorship suggested by the International Committee of Medical Journal Editors (www.icmje.org) and contributions of authors [53].

5.4. Current and future research efforts

In the near future, a standardized guideline for updating CERs applicable across EPCs covering a range of health care interventions and treatment modalities is needed. This guideline could incorporate a stepwise use of selected updating strategies and methods that have been empirically shown as valid, reliable, and resource efficient. Ideally, such a guideline would include specific recommendations on three important dimensions: (a) setting updating priorities based on factors such as public health burden, severity of health condition, qualitative/quantitative updating signals, number of outdated KQs for a given CER, (b) clarifying the responsibilities and authorship (especially when authors of the original report change their institutional affiliations or are difficult to locate) for updating CERs, and (c) implementing the updating process (by considering (a) and (b)).

5.5. Key messages and significance of Publication 5

In the absence of empirically validated methods for updating SRs, this guidance article is an early attempt to help interested authors and organisations in keeping their CERs or SRs current. This document provides an initial framework for consistent conceptualisation and application of updating processes across individual scientists and organisations.

This paper was published in the *Journal of Clinical Epidemiology*. This journal is one of a higher impact factor biomedical methods journals (3.417). It belongs to two categories: 1) Health Care Sciences and Services and 2) Public, Environmental, and Occupational Health. In the first category, which includes a total of 88 journals, the *Journal of Clinical Epidemiology* ranks as the 10th (Q1 quartile). In the second category (165 journals), this rank is the 22nd (Q1 quartile).

This article has been cited 12 times since its publication in 2011 (in Scopus; 2nd December, 2016). The citing sources are journals covering areas of general medicine (*J Gen Intern Med, BMJ*), specialist clinical (*Pain Physician*), methodology (*J Clin Epidemiol*) and veterinary medicine (*Preventive Veterinary Medicine*).

6. Assessing the Need for Updating Systematic Reviews

Publication 6 (Appendix 5) - A surveillance system to assess the need for updating systematic reviews [38]

6.1. Introduction and study rationale

Rapid accumulation of new research findings has raised concern among organizations about how best to identify which reviews may be out of date and whether to update or simply remove the outdated review from their websites. To date, organizations and initiatives (e.g., Cochrane, DERP) have relied on time-based periodic updating policies that have proven to be problematic in terms of feasibility and efficiency [13, 14, 29, 40, 30]. The previous research demonstrated that reviews become obsolete at different rates [30, 29, 24], suggesting that a system of regular surveillance might be a more effective way of identifying potentially out-of-date reviews.

In order to build upon the previous research and address the above-mentioned limitations, the AHRQ supported the development of a regular surveillance system for assessing the need of updating all CERs under the agency's portfolio. This section describes the methodology and results of this monitoring system applied to 24 AHRQ-conducted CERs from June 2011 to November 2012 [38, 54].

6.2. Methods

Two EPCs of Southern California (the RAND, the USA) and the University of Ottawa (Canada) have jointly started piloting two methods ('the RAND' and 'the Ottawa') for assessing the need of updating of CERs [37, 24]. The RAND method relies on the combination of an abbreviated search, clinical expert opinion, safety alerts, and determination of the validity of the CER's individual conclusions (**Table 3**) [37]. The Ottawa method ascertains qualitative and quantitative signals in newly identified evidence (**Table 3**) [24]. A formal comparison of the RAND and Ottawa methods resulted in similar findings [55, 56]. A third EPC (ECRI institute) assisted in obtaining safety alerts.

This surveillance system utilised the two methods jointly along with standard review process (**Figure 1**): a) abbreviated electronic searches (using the same strategy employed in the original CER, but limited to five general medicine journals and five specialty journals specific to the topic of the CER), b) study selection using the same criteria as in the original CER, c) data extraction of new evidence deemed relevant to the KQs of the original CER, d) identification of pre-specified qualitative and quantitative signals for updating, e) acquiring clinical expert opinion regarding the validity of conclusions in a CER, and f) identification of safety alerts relevant to the CER.

For each included new study, I or another reviewer extracted relevant data on study characteristics, participant socio-demographic factors, treatment, and outcome characteristics into evidence tables. For each conclusion, we first documented the absence or presence of new evidence meeting the pre-defined criteria of signal(s) indicating a need for updating (**Table 3**). We then assessed whether the new evidence contributed a qualitative signal (e.g., opposing findings, a superior new treatment).

Table 3. Criteria for determining that a conclusion is out-of-date in a systematic review (or comparative effectiveness review)

RAND method	
1	**Abbreviated search** Searches used in the original published CERs, the sources searched limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, The Lancet, and New England Journal of Medicine) and five topic-specific specialty journals (usually the journals that contributed the most evidence to the original report. These searches were conducted for a time period starting six months prior to the last date covered by the searches for the original CER (to minimize the number of relevant studies missed due to delayed publication) up to the present
1	**Clinical expert opinion** We identified and contacted two sets of clinical experts: a) those who had worked on the CER in question (e.g., the project lead, clinical lead, members of the technical expert panel, and peer reviewers) and b) other clinical experts in the clinical content area who had not worked on the CER in question (e.g., local or external subject matter experts). For each CER, we created a matrix that included each of the original key questions and a summary of each conclusion in the original report. Respondents were asked to provide their opinions on whether or not each conclusion was still valid. They were also asked to provide references for any new studies they were aware of that might invalidate or otherwise alter the conclusion(s) as well as studies that were pertinent to the topic but might not address a particular conclusion directly (e.g., studies of newer treatments that may have rendered the original treatments out-of-date). The responding experts were offered a small honorarium; reminders were sent to experts who did not initially respond
1	**Safety alerts**

	We examined safety and adverse event alerts relevant to each CER. This information was collected from the US FDA Safety Information and Adverse Event reporting system (MedWatch), the UK's MHRA, and Health Canada.
	Indications for the need for an update (per conclusion) – additional file 1 [38]
1	Original conclusion is still valid and this portion of the original report does not need updating. This conclusion was reached if we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid
2	Original conclusion is possibly out-of-date and this portion of the original report may need updating. This conclusion was reached if we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out-of-date
3	Original conclusion is probably out-of-date and this portion of the original report may need updating. This conclusion was reached if we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the
4	CER conclusion as probably out-of-date Original conclusion is out-of-date. This conclusion was reached if we found new evidence that rendered the CER conclusion out-of-date or no longer applicable; we classified the CER conclusion as out-of-date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out-of-date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, and so on
	Consideration for assigning the updating priority to a CER – additional file 1 [38]
1	How many conclusions of the CER are up-to-date, possibly out of date, or certainly out of date?
2	How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)
	Ottawa method
	Qualitative criteria for potentially invalidating signals
A1	Opposing findings: a pivotal* trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier
A2	Substantial harm: a pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision-making
A3	A superior new treatment: a pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm
	Qualitative criteria for signals of major changes
A4	Important changes in effectiveness short of 'opposing findings'
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant MA or non-pivotal trial
	Quantitative criteria signals of changes in evidence
B1	A change in statistical significance (from nonsignificant to significant or vice versa)
B2	A change in relative effect size of at least 50%
CER=comparative effectiveness review; FDA=Food and Drug Administration; MHRA=Medicines and Health Care Products Regulatory Agency; MA=meta-analysis	

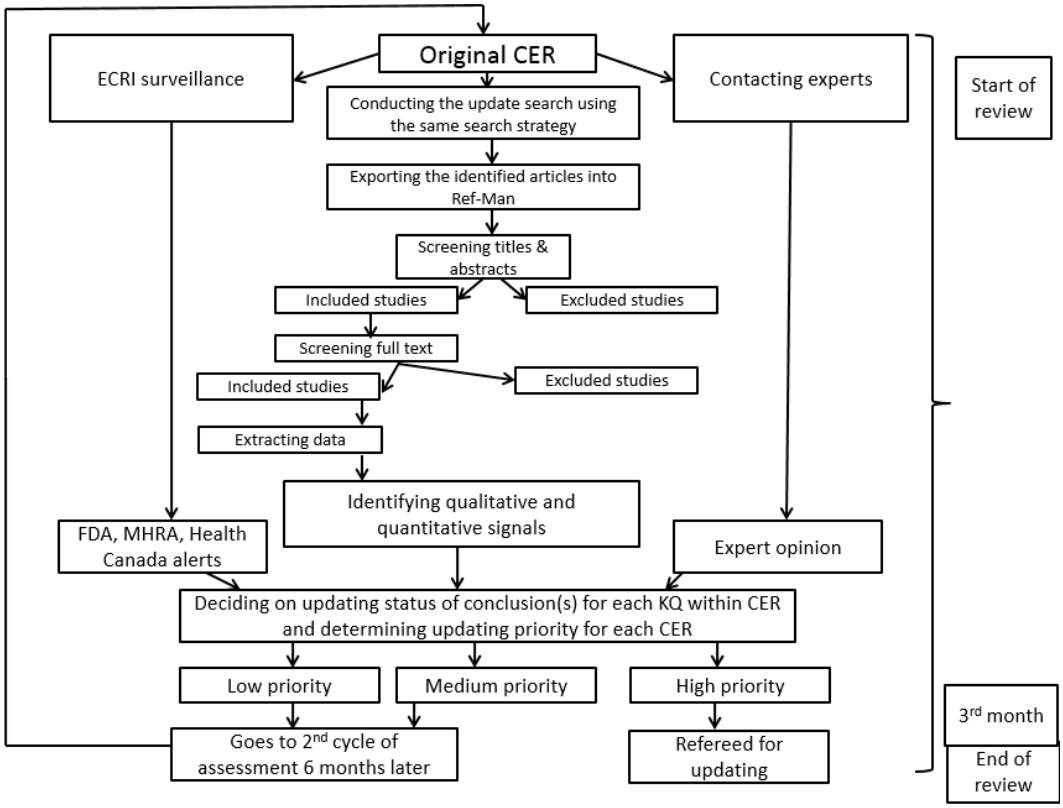
*a pivotal trial is defined as trial that is published in one of the top five general medical journals or a trial whose sample size is at least triple that of the largest trial in the original systematic review.

The presence of qualitative signal(s) were evaluated through incorporating results from a new study into a MA of the original CER (change in statistical significance, relative effect size change ≥50%). The information on updating signals, expert

opinion, and safety alerts was collated, summarized, and tabulated. Based on the evidence collated, we used a set of decision rules (**Table 3**) and categorized each KQ-specific conclusion within a CER as up-to-date, possibly out-of-date, probably out-of-date, or out-of-date. Then, using the totality of these characterizations and pre-specified criteria (e.g., how many conclusions out-of-date, how out-of-date, magnitude of change in effect estimate, black box warning), each CER was assigned a high, medium, or low updating priority (**Table 3**).

The CERs assigned a low or medium priority for updating were re-assessed six months later and those assigned a high priority were not reassessed and instead were referred for updating by considering the availability of resources and other factors when making a final decision (**Figure 1**).

Figure 1. The process of surveillance assessment of the need for updating comparative effectiveness reviews (CERs)



CER=comparative effectiveness review; FDA=Food and Drug Administration; MHRA=Medicines and Health Care Products Regulatory Agency; KQ=key question

We summarized our findings for each of the CERs in brief mini-reports. These reports are now posted on the AHRQ website along with the original CERs to which they refer (https://effectivehealthcare.ahrq.gov/). Two examples of these mini-reports adapted for this dissertation are provided in Appendix 5.

6.3. Results

Twenty-four CERs were assessed at least once between June 2011 and November 2012. The characteristics of these CERs and the corresponding surveillance assessments are presented in Publication 5 (Table 2). The number of KQs across CERs ranged from three to seven. The median number of included studies in the original CERs was 104 (interquartile range: 71 to 124) and the median number of newly identified studies relevant to the CERs was 15 (range: 0 to 35). The median length of time (in months) that had elapsed between the search conducted for the CER and the update surveillance search (search time lapse, STL) was 21 (range: 11 to 62). The number of experts initially contacted ranged from four to 17, with a median response rate of 35%.

Of 24 CERs, two (8%), five (21%), and 17 (71%) were assigned high, medium, and low priority for updating, respectively. Although a higher updating priority was associated with a longer STL and greater number of new relevant articles, still there was a substantial overlap, and no threshold existed for either factor that could accurately predict the classification of CERs into updating categories. We identified nine safety alerts applicable to 24 CERs. None of the agents, devices, or procedures evaluated in the 24 CERs had an FDA black box warning (indicating a significant risk of serious or even life-threatening adverse effect) issued during our assessment period. In only one case was the updating priority of a CER influenced by a safety alert.

6.4. Key messages and significance of Publication 6

The reviewed evidence suggests that the optimal interval for surveillance is yearly. Our results indicate that a small proportion of AHRQ-supported SRs may need updating within one to two years of the date of their last search.

Optimally timed surveillance for assessing the need of updating individual SRs may be a more efficient approach compared to updating them based on a fixed-time period, simply because SRs get out-of-date at different rates depending on the pace of development in literature, emergence of quantitative and qualitative signals, and other factors (e.g., available resources, strength of evidence, healthcare burden, nature of the condition). The implementation of the surveillance assessment program to determine the currency of published AHRQ-supported SRs was not without challenges and limitations which included subjective nature of judgements regarding the currency of CERs, differences across reports in the ways conclusions were presented, low response rates among clinical experts contacted, and delays in the release of the original reports themselves. The assessment of need for updating of more complex CERs (with multiple KQs and conclusions) was more cumbersome and time-consuming to complete, ranging up to 5 months.

By undertaking periodic evaluation of 24 topically diverse AHRQ-commissioned CERs, we established the feasibility of a surveillance system to monitor the currency of SRs of a wide range of therapeutic interventions. Following this demonstration, the AHRQ's EPCs have been using the Ottawa-RAND surveillance method for assessing the need for updating their CERs in prioritising the updating process across the organisation. This methodology is equally applicable to SRs with or without MA. Other non-AHRQ organisations may find this methodology useful to use it, since it is also applicable to non-AHRQ SRs.

For future research, we recommend: 1) modifying and testing the current surveillance methodology to encompass reviews of diagnostic and prognostic methods, 2) identifying predictors of a review being out-of-date, and 3) assessment of the relationship between the quality or strength of evidence and signal detection.

This paper was published in the *Systematic Reviews*. Although this journal has been established very recently (2011), it has published many influential research papers in the field of methodology. The focus of the journal covers many aspects of the design, conduct and reporting of SRs. The journal publishes high quality SR products including SR protocols, SRs related to a very broad definition of health, rapid

reviews, updates of already completed SRs, and methods research related to the science of SRs, such as decision modelling.

This article has been cited eight times since its publication in 2013 (in Scopus; 2nd December, 2016). The citing sources are journals covering areas of general medicine (*JAMA*), specialist clinical (*Eur J Orthod*), and methodology (*Stat Med, Syst Rev*).

7. Current and Future Research: Challenges and Perspectives

7.1. Recent progress in methods for updating systematic reviews

Three empirical methodologic studies and two conceptual works (presented in six publications) overviewed in this essay identified important gaps in knowledge and laid a groundwork for more research in the field of updating and keeping SRs current. This work is expected to inform future research and policy on updating SRs as well as maintaining them up-to-date.

Our formal definition of what constitutes an update of SR (Publication 1)[12] has been adopted by Cochrane and the high number of citations is indicative of an increasing uptake of this definition by the international scientific community. My subsequent collaborative works, both a systematic review of methods and strategies used for updating SRs (Publications 2 and 3) [41, 7] and the international survey of agencies involved in conduct or commissioning of SRs (Publication 4)[13] highlighted the dearth of adequate and efficient methods for updating SRs as well as inconsistencies in beliefs on updating and updating practices. My next article (Publication 5) provided a general guidance on updating and highlighted the challenges of authorship of updating SRs among others [14]. Finally, our surveillance study for assessing the need for updating CERs showed that updating SRs could be prioritised efficiently, suggesting that priority-based updating may be more efficient and feasible than updating of all SRs periodically (Publication 6)[38].

In the past decade, more attention, work, and resources have been devoted to the issue of updating. Specifically, more methods informing when (or how frequently) it is best to update any given review and empirical results comparing these methods have emerged. This is an obvious methodological improvement in terms of efficient use and allocation of limited resources compared to the allowance of fixed period(s) of time to an update without considering many other factors affecting the need for updating (e.g., public health burden, updating qualitative and quantitative signals identified, and bibliometric measurements).

For example, Cochrane has initiated important steps towards prioritising the updating process. Namely, one of the key milestones of Cochrane's Strategy 2020

(2016 Targets) has been to develop and implement a comprehensive updating strategy to ensure that all high priority Cochrane reviews are kept up-to-date. Cochrane has worked on the methodology for prioritising their reviews for updating as described by the Cochrane Neonatal Review Group [39]. This was followed by the development of the Cochrane multicomponent decision tool for prioritising the updating of SRs [40]. This tool is more comprehensive compared to those described in our previous work (Publication 2) [7], since it incorporates both qualitative and quantitative signals needed to be considered when updating SRs. The tool provides a structured way of identifying SRs whose conclusions are most prone to change. The tool consists of a flow chart with decision-making branches (three steps with respective questions): step one (is the clinical question already answered or deemed no longer relevant?), step two (are there any new factors relevant to the existing review?), and step three (are there new studies?). Reasons for decisions made at each step (e.g., don't update, flag review 'priority for updating', update now) should be provided. The Cochrane Airways Group (CAG) piloted the tool's performance on 21 [40] and later on 270 CAG reviews, of which 30 were successfully prioritised as in need of updating [57].

Most recently, Cochrane has drawn on previous research and experience to develop a formal consensus-based guideline and checklist informing when and how to update SRs.[58] The statements and issues on updating SRs covered in the Cochrane guideline are in line with those highlighted in our previous research published in the six articles (e.g., the definition, methods of prioritisation, new SR methods, authorship, reporting changes). It is worth noting that the panel for updating guidance (PUG) expanded the previous definition of an update of a SR (Publication 1)[12] as follows: "*a new edition of a published systematic review with changes that can include new data, new methods, or new analyses to the previous edition*." In Cochrane, the decision regarding when to update any given SR is decentralised, meaning that it is delegated to the CRG. This is in contrast with the AHRQ where this decision is centralised and the prioritisation of CER updates is based on the surveillance assessments of the need for updating, as described in one of our six publications (Publication 6)[38]. The Cochrane decision algorithm for updating SRs consists of a series of signalling questions assigned to the following three steps: step one (e.g., does a SR still address a current question?), step two (are there any new

relevant methods; are there any new studies or new information?), and step three (e.g., will the adoption of new methods or inclusion of new studies, information or data change findings or credibility?). If the answer to all three steps is 'yes' or 'yes or maybe', it is recommended that a SR be updated. The PUG suggests to update a SR if newly available methods (e.g., for assessing risk of bias in primary studies, grading evidence, pooling studies) are likely to improve the quality of the SR. This is consistent with the recommendations from previous research by Mayhew et al. [59] which discussed the evolvement of Cochrane's Risk of Bias (RoB) tool for RCTs [60]. The authors advised that while updating a review, the original RoB assessments (done using early version of the tool) of included RCTs be replaced with those using the most recent version of the tool. This approach ensures methodological currency and facilitates consistency of assessments and reporting within and across reviews. This recommendation is also in line with that presented in our earlier work suggesting to re-assess the previously synthesised and new evidence using a newer methodology, provided the new methodology is an improvement over the older version (Publication 5) [14]. Finally, the Cochrane PUG recommend that reviewers use efficient search methods reflecting or adjusted for any changes in the research question and inclusion criteria as well as innovative technologies helping to streamline the review process (e.g., automation technology, machine-learning text-mining software)[58].

Recent studies have provided additional empirical evidence by comparing the performance of methods in informing when (or how frequently) to update a SR. For example, one study demonstrated a good agreement between the Barrowman's method (identifying null MAs that are ripe for updating) [43] and a new simulation-based method [61] in prioritising 12 MAs' updates under certain conditions (homogeneity, new studies consistent with those already included in a meta-analysis) [62]. Similarly, in a recent empirical study [63], five statistical methods and their extensions were compared in identifying out-of-date meta-analyses in 80 SRs published by the Cochrane Pregnancy and Childbirth Group between 2008 and 2010. The methods compared were: a) recursive CMA [48], b) CMA for sufficiency and stability [46], c) Barrowman's test for identifying null meta-analyses that are ripe for updating [43], d) Ottawa method (quantitative signal of changes in evidence) [24], and e) the power of an updated MA using simulation-based power method) [61]. The

Ottawa method found 34 reviews as out-of-date versus seven found by using each the recursive CMA and Barrowman method. Two methods (CMA for sufficiency and stability and simulation-based power method) did not label any review as out-of-date.

7.2. Facilitating updating process

Notwithstanding the recent methodologic developments, updating and keeping SRs up-to-date remains a challenging process. The absence of appropriate methodology, limited resources available, lack of publishing outlets and academic incentives alone or combination may be responsible for many SRs remaining out-of-date.

There is a wide variability across studies in when SRs become out-of-date, ranging from 2 to 6 years, which may be explained by multifactorial nature and complexity of updating as a construct (e.g., the pace of development in literature, emergence of quantitative and qualitative signals, available resources, strength of evidence, healthcare burden, nature of the condition). Therefore, currently there is no fast and accurate decision tool or approach, which would help to predict when any SR becomes out-of-date or determine the most optimal time when to update a SR. Decision tools for updating, including regression-based algorithms that consider the multifactorial nature of the updating construct need to be developed and validated.

In order to extend the currency of SRs, more efforts should be put towards reducing the time needed to produce and publish SRs [4]. Besides using the methods for expediting the conduct of SRs, authors are recommended to update their searches prior to submission for publication consideration; this increases a life-span of an updated review. Moreover, publishers outside Cochrane should accelerate the peer-review process. For example, Sampson et al. [34] explored 154 reviews (91 non-Cochrane, 36 Cochrane, 27 technical reports) and found the median time-lag from the last search to publication was 61 weeks (inter-quartile range: 33-87), with a longer median time-lag for non-Cochrane journal vs. Cochrane reviews (65 weeks vs. 31 weeks). The median time from the last search to indexing was 74 weeks (inter-quartile range: 52-108).

In general, the updating process could be facilitated using modified but validated methods by restricting or bypassing any given SR step(s) (e.g., eligibility criteria, search strategy, study selection, data extraction, or quality assessment) [4, 64]. The use of such abbreviated methods including those for so called 'rapid reviews' have been extensively discussed [65-69]. More empirical evidence suggests that certain resource-efficient or abbreviated techniques applied to any given review step (e.g., inclusions criteria, search strategy) could be used while updating reviews [36, 70-73]. For example, one efficient approach that can inform the updating process is a forward citation search. This technique involves the identification of new relevant evidence (e.g., SRs, primary studies) that cited the SR being updated or primary studies included in this SR. The use of forward citation searching alone will have a lower recall rate than the full update search of the original SR search, since not all relevant studies or SRs will cite the SR in question. However, this problem is likely to be minimised as more journals and funding agencies require that primary study authors consider (and consequently cite) relevant prior SRs to inform the design and ethical aspects of their studies. Meanwhile, it is advisable that forward citation searching be used in conjunction with other searches. Forward citation searching can be performed in Google Scholar, Web of Science, and other search platforms (e.g., CINAHL, PsycINFO, Social Sciences Citation Index, and Arts & Humanities Citation Index).

Another example of the abbreviated technique applied in the updating context was our surveillance study, which used abbreviated search strategy (limited to five general and five topic-specific specialty medical journals) and a single-reviewer study screening and data extraction to assess the need for updating of 24 CERs by assigning them to low, medium, and high priority groups for updating (Publication 6)[38]. This surveillance method proved to be an efficient and valid approach for updating SRs. In a recent study, Shekelle and colleagues assessed the validity of this surveillance method applied to nine CERs in 2009 against 'changes/no changes' in conclusions due to a complete updating of all nine CERs done in 2013[74]. Specifically, for each CER conclusion, the authors evaluated the degree of congruence (good, fair, poor) between the 2009 classifications predicted (low, medium, high priority for updating) and the magnitude of change in conclusions

after the actual update was done in 2013. The findings demonstrated a good concordance for 83% and good or fair concordance for 99% of the CER conclusions.

Current developments in machine learning-based automation (or semi-automation) used in the SR production can be considered as another factor to benefit the feasibility and efficiency of updating process [4]. For example, several studies demonstrated reduced workload (>50%) [75, 76] and high recall rates (>70%) [77, 78] in identifying and screening new potentially relevant studies using automation of citation tracking [77], alerts for newly emerged potentially relevant to SR publications [78], and article classification for its inclusion into a SR [76, 75].

Today's technological advances have made it possible to develop and evaluate new publication formats that could facilitate the updating process. Elliott and colleagues [79] introduced 'living SRs,' which are high quality online evidence summaries, continuously updated as new relevant evidence becomes available. This product is a dynamic and constantly changing online-only evidence summary which demands less efforts and time compared with static and sporadically updated more resource-intensive conventional SRs. Similarly, Shanahan points out the limitations of the traditional publication 'static' format and advocates creation of a single evolving document for a study (starting with registration, to protocol, and extending to results as they become available), which would allow a prospective and transparent evaluation based on the hypothesis and reliable assessment of bias or selective reporting [80].

Making authors responsible for updating their SRs periodically had shown some compliance within Cochrane, but not outside Cochrane [39]. In agreement, the findings of our international survey on updating showed Cochrane authors to be more committed to updating their reviews than those of non-Cochrane reviews (Publication 4) [13]. Also, our findings are in line with those from a more recent survey of barriers to updating (e.g., insufficient resources, lack of reviewer motivation, no academic credit, limited publishing formats, insufficient time, inability to publish SR updates in peer-reviewed journals) [33]. This survey, which was based on the sample of 181 SRs identified from the American College of

Physicians (ACP) Journal Club 2007-2008 issues, demonstrated the lack of sufficient resources (74.6%) and inability to publish (52.2%) as barriers to updating. Authors spending more than 25% of their time dedicated to SRs were more likely to update their review (OR=7.25, 95% CI: 1.45, 35.71) [33].

Academic institutions can support updating by according academic recognition on par with publishing original SRs. Journals can increase publishing outlets for updates, for instance, when accepting a review for publication, by also committing to publishing any future updates. Organizations can make updates more prominent by tying them to the original review (Publication 4) [13]. For example, the Public Library of Science (PLoS) electronically links SR updates to freely available original reports [81].

One barrier to updating is a change in authorship taking place between the original publication and an update or between two updates of a review. Jaidee and colleagues showed that reviews updated by the original authors took a far shorter median number of years compared to those updated by a new review team (2.5 vs. 8.6) [27]. Although it is recommended that a review be updated by the original review authors, this is often not possible for various reasons (Publication 5) [14]. Within Cochrane, authors who do not intend on updating their review are suggested to team with other authors or turn the review over to other interested authors [39]. The Cochrane PUG do not provide any specific clear-cut guidance regarding the authorship in relation to SR updates [58].

Finally, harmonisation of updating efforts may be another approach for organisations to cooperate in updating, sharing resources and knowledge on issues of surveillance, conduct, reporting and policy for updating. The harmonisation of updating was supported by the majority of organisations responding to our survey, but such cooperation may be in its infancy (Publication 4) [13]. One activity of such harmonisation may be an establishment and maintenance of a registry for updated SRs linked to an international prospective register for SR protocols (PROSPERO; www.crd.york.ac.uk/PROSPERO/), administered by the Centre for Reviews and Dissemination (CRD). The availability of such registry would help to reduce the

overlap or unnecessary duplication across review updates and research waste [82, 83].

7.3. Future developments in updating systematic reviews

In light of the continuously growing body and type of evidence, considerably more investments should be made available to further investigate issues surrounding the methodology of updating and keeping SRs up-to-date. More research should be devoted to the identification of clinical, statistical, or methodological predictors for the need of updating SRs. The exploration of differences in the rates of literature growth across clinical fields, using bibliometric methodology, is likely to provide a better understanding of the practical implications of different approaches to updating SRs.

Future research needs to optimise the presentation for updates of evidence synthesis products. Given that users of SRs (e.g., researchers, physicians, policy makers, or patients) differ in their preferences as to how updated reviews should be formatted and presented, some consideration should be given to multiple ways of presentation of the same update information using graphics, tables, text, and figures. Newberry and colleagues [84] collected and analysed an input from different stakeholders regarding the usability of five different formats of executive summaries of updated CERs. The authors found that policy makers preferred to see clearly marked changes in review process and outcomes as well to have access to data analyses with corresponding conclusions. Physicians preferred to see the skeleton of the review including KQs, inclusion criteria, outcomes, and conclusions provided graphically. Ideally, the effective presentation of an update should be supplemented by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) study flow diagram [85] depicting study selection processes for the original review as well as the review update. Based on multiple working group feedback and recommendations, Stovold and colleagues produced an adapted PRISMA flow diagram for a review update [86]. Additional research is warranted to formulate guidelines and checklist for reporting updated SRs as an extension of PRISMA.

Other existing gaps in the evidence warranting future research are methods for updating qualitative reviews [87] as well as those for updating relatively novel types of quantitative data synthesis products such as reviews of individual participant data (IPD) [88] and network meta-analysis (NMA) [89, 90].

Similarly, it might be worthwhile exploring the application of methods developed in different fields for their potential utility to inform when and/or how to update SRs. For example, economists developed the Value-of-Information analysis (VOI) [91]. Using this approach, it may be assumed that there is some value in updating (even if the results of the review remain unchanged), the value which relates to the reduced uncertainty associated with decision-making favouring the option of updating. Thus, the value of information corresponding to any update of a SR would indicate the appropriateness of updating seen as a trade-off between the resources required and the magnitude of the reduction in uncertainty associated with any further information. Thus, the VOI analysis applied to an updating decision would allow the calculation of the cost-effectiveness ratio for updating any given review (i.e., the ratio of total costs associated with updating per expected net benefit to a population from updating a review). Then, reviews could be ranked in order of increasing cost-effectiveness ratios which would correspond to decreasing updating priority [92].

Updating SRs will have an important role in future in increasing the value of and reducing waste from scientific research. In their viewpoint "Avoidable waste in the production and reporting of research evidence", Chalmers and Glasziou estimated that up to 85% of research investment was 'avoidably' wasted [93]. The highlighted areas were poorly formulated research questions, inappropriate study design, selective publication, and inadequate reporting of research findings. In 2014, the Lancet published a series of articles whose authors provided recommendations as how to increase efficiency in conducting research and reduce the research waste [83, 94-98]. In this context, updating and maintaining SRs current can be conceptualised as an input process by using efficient approaches (e.g., abbreviated methodology, innovative automation technologies) leading to an output of a research product with improved quality (i.e., updated SR). Recently, Créquit et al., demonstrated an example of research waste [99]. The authors conducted a living cumulative NMA of RCTs of second-line treatments for advanced lung cancer and showed that this

evidence in SRs was incomplete and out-of-date, with missing at least 40% of treatments, 38% of treatment comparisons, and 45% of trials. The authors suggested a continuously updated (i.e., living cumulative) NMA for a more complete and updated evidence presentation as a means of reducing the waste of research.

In conclusion, beyond the goal of publishing a SR, is the need to keep its evidence base up-to-date. This is likely a shared scientific and ethical obligation, although exactly whose responsibility this is, is not immediately clear. Perhaps it should be a joint responsibility between the investigators conducting the SR, the journals publishing the reviews, and the commissioning agencies requesting them. More concerted research efforts are required to illuminate further knowledge gaps in the field of updating SRs. Similarly, more efforts are required to ascertain the potential benefits of developing geographically harmonized, efficient, yet valid ways of updating SRs. Ideally, the updating process, apart from the available resources, should also consider issues related to search strategy, clinical questions, public health, and statistical techniques to accurately reflect the complexity of the ever-evolving evidence.

8. References

1. Higgins JP, Green S, Scholten RJ. Maintaining Reviews: Updates, Amendments and Feedback. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. 2008. p. 31-49.

2. Mulrow CD. Rationale for systematic reviews. BMJ (Clinical research ed). 1994;309(6954):597-9.

3. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Annals of internal medicine. 1997;126(5):376-80.

4. Tsertsvadze A, Chen YF, Moher D, Sutcliffe P, McCarthy N. How to conduct systematic reviews more expeditiously? Systematic reviews. 2015;4(1):160. doi:10.1186/s13643-015-0147-7.

5. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Wiley Online Library; 2008.

6. Cook DJ, Greengold NL, Ellrodt AG, Weingarten SR. The relation between systematic reviews and practice guidelines. Annals of internal medicine. 1997;127(3):210-6.

7. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M et al. A systematic review identified few methods and strategies describing when and how to update systematic reviews. Journal of clinical epidemiology. 2007;60(11):1095-104. doi:10.1016/j.jclinepi.2007.03.008.

8. Tricco AC, Tetzlaff J, Moher D. The art and science of knowledge synthesis. Journal of clinical epidemiology. 2011;64(1):11-20. doi:10.1016/j.jclinepi.2009.11.007.

9. Atkins D, Fink K, Slutsky J, Agency for Healthcare R, Quality, North American Evidence-based Practice C. Better information for better health care: the Evidence-based Practice Center program and the Agency for Healthcare Research and Quality. Annals of internal medicine. 2005;142(12 Pt 2):1035-41.

10. Habre C, Tramer MR, Popping DM, Elia N. Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection. BMJ (Clinical research ed). 2014;348:g5219. doi:10.1136/bmj.g5219.

11. Vergnes JN, Marchal-Sixou C, Nabet C, Maret D, Hamel O. Ethics in systematic reviews. Journal of medical ethics. 2010;36(12):771-4. doi:10.1136/jme.2010.039941.

12. Moher D, Tsertsvadze A. Systematic reviews: when is an update an update? Lancet. 2006;367(9514):881-3. doi:10.1016/S0140-6736(06)68358-X.

13. Garritty C, Tsertsvadze A, Tricco AC, Sampson M, Moher D. Updating systematic reviews: an international survey. PLoS ONE [Electronic Resource]. 2010;5(4):e9914.

14. Tsertsvadze A, Maglione M, Chou R, Garritty C, Coleman C, Lux L et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. Journal of clinical epidemiology. 2011;64(11):1208-15. doi:10.1016/j.jclinepi.2011.03.011.

15. Chalmers I, Enkin M, Keirse MJ. Preparing and updating systematic reviews of randomized controlled trials of health care. The Milbank quarterly. 1993;71(3):411-37.

16. Chalmers I, Haynes B. Reporting, updating, and correcting systematic reviews of the effects of health care. BMJ (Clinical research ed). 1994;309(6958):862-5.

17. Stead LF, Lancaster T, Silagy CA. Updating a systematic review--what difference did it make? Case study of nicotine replacement therapy. BMC medical research methodology. 2001;1:10.

18. Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. The Cochrane database of systematic reviews. 2007(2):MR000011. doi:10.1002/14651858.MR000011.pub2.

19. Shea B, Boers M, Grimshaw JM, Hamel C, Bouter LM. Does updating improve the methodological and reporting quality of systematic reviews? BMC medical research methodology. 2006;6:27. doi:10.1186/1471-2288-6-27.

20. Pieper D, Antoine SL, Neugebauer EA, Eikermann M. Up-to-dateness of reviews is often neglected in overviews: a systematic review. Journal of clinical epidemiology. 2014;67(12):1302-8. doi:10.1016/j.jclinepi.2014.08.008.

21. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS medicine. 2010;7(9):e1000326. doi:10.1371/journal.pmed.1000326.

22. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS medicine. 2007;4(3):e78. doi:10.1371/journal.pmed.0040078.

23. 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 medicine. 2016;13(5):e1002028. doi:10.1371/journal.pmed.1002028.

24. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Annals of internal medicine. 2007;147(4):224-33.

25. French SD, McDonald S, McKenzie JE, Green SE. Investing in updating: how do conclusions change when Cochrane systematic reviews are updated? BMC medical research methodology. 2005;5:33. doi:10.1186/1471-2288-5-33.

26. Higgins J. How should we interpret updated meta-analyses? [abstract]. 7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy 1999.

27. Jaidee W, Moher D, Laopaiboon M. Time to update and quantitative changes in the results of cochrane pregnancy and childbirth reviews. PLoS ONE [Electronic Resource]. 2010;5(7):e11553.

28. Bastian H, Doust J. When does an updated meta-analysis have enough content to justify re-reading? [abstract]. XI Cochrane Colloquium: Evidence, Health Care and Culture; 2003 Oct 26-31; Barcelona, Spain 2003.

29. Chapman A, Middleton P, Maddern G. Early updates of systematic reviews - a waste of resources? 4th Symposium on Systematic Reviews: Pushing the Boundaries; 2002 Jul 2-4; Oxford, UK 2002.

30. Peterson K, McDonagh MS, Fu R. Decisions to update comparative drug effectiveness reviews vary based on type of new evidence. Journal of clinical epidemiology. 2011;64(9):977-84.

31. Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M et al. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. Jama. 1998;280(3):278-80.

32. Linde K. Updating systematic reviews. Explore. 2006;2(4):363-4. doi:10.1016/j.explore.2006.05.016.

33. Phung OJ, Baker WL, Baker EL, Coleman CI. Intent to update systematic reviews: results of an internet survey. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2011;59(5):811-5. doi:10.231/JIM.0b013e3182124c75.

34. Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, Moher D. Systematic reviews can be produced and published faster. Journal of clinical epidemiology. 2008;61(6):531-6. doi:10.1016/j.jclinepi.2008.02.004.

35. Henderson S, Hampson L, Atherton D, Neilson J. Ten years of updating Cochrane reviews: the experiences of the Pregnancy and Childbirth Group [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland 2006.

36. Sampson M, Shojania KG, McGowan J, Daniel R, Rader T, Iansavichene AE et al. Surveillance search techniques identified the need to update systematic reviews. Journal of clinical epidemiology. 2008;61(8):755-62. doi:10.1016/j.jclinepi.2007.10.003.

37. Shekelle P, Newberry S, Maglione M, Shanman R, Johnsen B, Carter J et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009). AHRQ Methods for Effective Health Care. Rockville (MD)2009.

38. Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S et al. A surveillance system to assess the need for updating systematic reviews. Systems Review. 2013;2:104.

39. Soll RF. Updating reviews: the experience of the Cochrane Neonatal Review Group. Paediatric and perinatal epidemiology. 2008;22 Suppl 1:29-32. doi:10.1111/j.1365-3016.2007.00909.x.

40. Takwoingi Y, Hopewell S, Tovey D, Sutton AJ. A multicomponent decision tool for prioritising the updating of systematic reviews. BMJ (Clinical research ed). 2013;347:f7191. doi:10.1136/bmj.f7191.

41. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M et al. When and how to update systematic reviews. The Cochrane database of systematic reviews. 2008(1):MR000023. doi:10.1002/14651858.MR000023.pub3.

42. Helfand M, Balshem H. AHRQ series paper 2: principles for developing guidance: AHRQ and the effective health-care program. Journal of clinical epidemiology. 2010;63(5):484-90. doi:10.1016/j.jclinepi.2009.05.005.

43. Barrowman NJ, Fang M, Sampson M, Moher D. Identifying null meta-analyses that are ripe for updating. BMC medical research methodology. 2003;3:13. doi:10.1186/1471-2288-3-13.

44. Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H, Jr., Fagerstrom RM. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls. The New England journal of medicine. 1981;305(14):795-9. doi:10.1056/NEJM198110013051404.

45. Borm GF, Donders AR. Updating meta-analyses leads to larger type I errors than publication bias. Journal of clinical epidemiology. 2009;62(8):825-30 e10. doi:10.1016/j.jclinepi.2008.08.010.

46. Muellerleile P, Mullen B. Sufficiency and stability of evidence for public health interventions using cumulative meta-analysis. American journal of public health. 2006;96(3):515-22. doi:10.2105/AJPH.2003.036343.

47. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Controlled clinical trials. 1997;18(6):580-93; discussion 661-6.

48. Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. Journal of clinical epidemiology. 1999;52(4):281-91.

49. Shekelle P, Eccles MP, Grimshaw JM, Woolf SH. When should clinical guidelines be updated? BMJ (Clinical research ed). 2001;323(7305):155-7.

50. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? Jama. 2001;286(12):1461-7.

51. Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of clinical epidemiology. 2011;64(11):1168-77. doi:10.1016/j.jclinepi.2010.11.022.

52. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ (Clinical research ed). 2005;331(7524):1064-5. doi:10.1136/bmj.38636.593461.68.

53. Rennie D, Flanagin A, Yank V. The contributions of authors. Jama. 2000;284(1):89-91.

54. Newberry SJ, Ahmadzai N, Motala A, Tsertsvadze A, Maglione M, Ansari MT et al. AHRQ Methods for Effective Health Care. Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

55. Shekelle PG, Newberry SJ, Wu H, Suttorp M, Motala A, Lim YW et al. AHRQ Methods for Effective Health Care. Identifying Signals for Updating Systematic Reviews: A Comparison of Two Methods. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.

56. Chung M, Newberry SJ, Ansari MT, Yu WW, Wu H, Lee J et al. Two methods provide similar signals for the need to update systematic reviews. Journal of clinical epidemiology. 2012;65(6):660-8. doi:10.1016/j.jclinepi.2011.12.004.

57. Welsh E, Stovold E, Karner C, Cates C. Cochrane Airways Group reviews were prioritized for updating using a pragmatic approach. Journal of clinical epidemiology. 2015;68(3):341-6. doi:10.1016/j.jclinepi.2014.11.002.

58. Garner P, Hopewell S, Chandler J, MacLehose H, Schunemann HJ, Akl EA et al. When and how to update systematic reviews: consensus and checklist. BMJ (Clinical research ed). 2016;354:i3507. doi:10.1136/bmj.i3507.

59. Mayhew AD, Kabir M, Ansari MT. Considerations from the risk of bias perspective for updating Cochrane reviews. Systematic reviews. 2015;4:136. doi:10.1186/s13643-015-0122-3.

60. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928. doi:10.1136/bmj.d5928.

61. Sutton AJ, Cooper NJ, Jones DR, Lambert PC, Thompson JR, Abrams KR. Evidence-based sample size calculations based upon updated meta-analysis. Statistics in medicine. 2007;26(12):2479-500. doi:10.1002/sim.2704.

62. Sutton AJ, Donegan S, Takwoingi Y, Garner P, Gamble C, Donald A. An encouraging assessment of methods to inform priorities for updating systematic reviews. Journal of clinical epidemiology. 2009;62(3):241-51. doi:10.1016/j.jclinepi.2008.04.005.

63. Pattanittum P, Laopaiboon M, Moher D, Lumbiganon P, Ngamjarus C. A comparison of statistical methods for identifying out-of-date systematic reviews. PLoS ONE [Electronic Resource]. 2012;7(11):e48894.

64. Knottnerus JA, Tugwell P. Knowledge synthesis to improve practice requires up-to-date definitions, content, methods, and techniques. Journal of clinical epidemiology. 2014;67(12):1289-90. doi:10.1016/j.jclinepi.2014.10.009.

65. Harker J, Kleijnen J. What is a rapid review? A methodological exploration of rapid reviews in Health Technology Assessments. International journal of evidence-based healthcare. 2012;10(4):397-410. doi:10.1111/j.1744-1609.2012.00290.x.

66. Hartling L, Guise JM, Kato E, Anderson J, Aronson N, Belinson S et al. EPC Methods: An Exploration of Methods and Context for the Production of Rapid Reviews. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2015.

67. Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implementation science : IS. 2010;5:56. doi:10.1186/1748-5908-5-56.

68. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Systematic reviews. 2012;1:10. doi:10.1186/2046-4053-1-10.

69. Polisena J, Garritty C, Umscheid CA, Kamel C, Samra K, Smith J et al. Rapid Review Summit: an overview and initiation of a research agenda. Systematic reviews. 2015;4:111. doi:10.1186/s13643-015-0111-6.

70. Sampson M, de Bruijn B, Urquhart C, Shojania K. Complementary approaches to searching MEDLINE may be sufficient for updating existing systematic reviews. Journal of clinical epidemiology. 2016. doi:10.1016/j.jclinepi.2016.03.004.

71. Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. International journal of technology assessment in health care. 2003;19(4):591-603.

72. Moher D, Pham B, Klassen TP, Schulz KF, Berlin JA, Jadad AR et al. What contributions do languages other than English make on the results of meta-analyses? Journal of clinical epidemiology. 2000;53(9):964-72.

73. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. International journal of technology assessment in health care. 2012;28(2):138-44. doi:10.1017/S0266462312000086.

74. Shekelle PG, Motala A, Johnsen B, Newberry SJ. Assessment of a method to detect signals for updating systematic reviews. Systematic reviews. 2014;3:13. doi:10.1186/2046-4053-3-13.

75. Dalal SR, Shekelle PG, Hempel S, Newberry SJ, Motala A, Shetty KD. A pilot study using machine learning and domain knowledge to facilitate comparative effectiveness review updating. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):343-55. doi:10.1177/0272989X12457243.

76. Wallace BC, Small K, Brodley CE, Lau J, Schmid CH, Bertram L et al. Toward modernizing the systematic review pipeline in genetics: efficient updating via data mining. Genetics in medicine : official journal of the American College of Medical Genetics. 2012;14(7):663-9. doi:10.1038/gim.2012.7.

77. Choong MK, Tsafnat G. Role of citation tracking in updating of systematic reviews. AMIA Joint Summits on Translational Science proceedings AMIA Summit on Translational Science. 2014;2014:18.

78. Cohen AM, Ambert K, McDonagh M. Studying the potential impact of automated document classification on scheduling a systematic review update. BMC Medical Informatics & Decision Making. 2012;12:33.

79. Elliott JH, Turner T, Clavisi O, Thomas J, Higgins JP, Mavergames C et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. PLoS medicine. 2014;11(2):e1001603. doi:10.1371/journal.pmed.1001603.

80. Shanahan DR. A living document: reincarnating the research article. Trials. 2015;16(1):151. doi:10.1186/s13063-015-0666-5.

81. Editors PLM. Many reviews are systematic but some are more transparent and completely reported than others. PLoS medicine. 2007;4(3):e147. doi:10.1371/journal.pmed.0040147.

82. Moher D. The problem of duplicate systematic reviews. BMJ (Clinical research ed). 2013;347:f5040. doi:10.1136/bmj.f5040.

83. Kleinert S, Horton R. How should medical science change? Lancet. 2014;383(9913):197-8. doi:10.1016/S0140-6736(13)62678-1.

84. Newberry SJ, Shekelle PG, Vaiana M, Motala A. AHRQ Methods for Effective Health Care. Reporting the Findings of Updated Systematic Reviews of Comparative Effectiveness: How Do Users Want To View New Information? Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

85. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.

86. Stovold E, Beecher D, Foxlee R, Noel-Storr A. Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram. Systematic reviews. 2014;3:54. doi:10.1186/2046-4053-3-54.

87. France EF, Wells M, Lang H, Williams B. Why, when and how to update a meta-ethnography qualitative synthesis. Systematic reviews. 2016;5(1):44. doi:10.1186/s13643-016-0218-4.

88. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ (Clinical research ed). 2010;340:c221. doi:10.1136/bmj.c221.

89. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(4):417-28. doi:10.1016/j.jval.2011.04.002.

90. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(4):429-37. doi:10.1016/j.jval.2011.01.011.

91. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. Health technology assessment. 2004;8(31):1-103, iii.

92. Hoomans T, Seidenfeld J, Basu A, Meltzer D. Systematizing the Use of Value of Information Analysis in Prioritizing Systematic Reviews. AHRQ Methods for Effective Health Care. Rockville (MD)2012.

93. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86-9. doi:10.1016/S0140-6736(09)60329-9.

94. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM et al. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65. doi:10.1016/S0140-6736(13)62229-1.

95. Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet. 2014;383(9912):166-75. doi:10.1016/S0140-6736(13)62227-8.

96. Al-Shahi Salman R, Beller E, Kagan J, Hemminki E, Phillips RS, Savulescu J et al. Increasing value and reducing waste in biomedical research regulation and management. Lancet. 2014;383(9912):176-85. doi:10.1016/S0140-6736(13)62297-7.

97. Chan AW, Song F, Vickers A, Jefferson T, Dickersin K, Gotzsche PC et al. Increasing value and reducing waste: addressing inaccessible research. Lancet. 2014;383(9913):257-66. doi:10.1016/S0140-6736(13)62296-5.

98. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet. 2014;383(9913):267-76. doi:10.1016/S0140-6736(13)62228-X.

99. Crequit P, Trinquart L, Yavchitz A, Ravaud P. Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer. BMC medicine. 2016;14(1):8. doi:10.1186/s12916-016-0555-0.