Updating Comparative Effectiveness Reviews

Key points

- **Identify when / if an update is necessary**
- **Use comprehensive searches to identify new evidence or evidence that was missed by the previous CER.**
- **Use the update process as an opportunity to update methods and correct errors in previous CERs.[Mike: Should the update process be used as the opportunity to correct errors? Shouldn't these be corrected sooner or, at least, shouldn't there be a process to mark the errors within the CER before it gets updated?]**
- **Integrate new evidence into the prior CER, or present the new evidence in a separate section.**
- **Discuss how new evidence changes results and/or conclusions of the prior CER. Tables that contrast previous and new conclusions can be very helpful.**

Background

To maintain relevance, systematic reviews (SRs) need to be regularly updated as new evidence is produced.[1-3] Lack of attention to updating may lead to conclusions becoming antiquated[Mike: even if something is "antiquated" it might still be valid. I would use another phrase here, perhaps "out of keeping with the evidence that has accumulated since the SR was done".], thus compromising health care policy decisions. This could result in wasted resources, provision of redundant or ineffective health care, failure to implement more effective health care, and possibly cause harm. Thus, it is clear that SRs need to remain up-to-date. However, there is little information about what proportion of SRs currently need updating, when to initiate updating, and how best to carry it out.

A sample of 300 published SRs drawn from one-month's worth of MEDLINE© citations (November 2004) reports that 17.7% of all SRs were reported to be updates of previously completed reviews. Almost one-third of the x Cochrane therapeutic reviews in the sample were updates, compared to only 2.4% of the x non-Cochrane reviews.[4]

In the absence of a standard method to determine when or how to update any given SR, some organizations have made recommendations about the frequency with which the evidence base needs to be updated. The Cochrane Collaboration has an established policy that reviews be assessed and updated every two years, or a commentary be added to explain why this is done less frequently.[5] However, updating all SRs based on an a priori time interval could result in inefficient use of resources, as diverse areas in medicine will vary in how frequently they need to be updated. The UK National Institute for Health and Clinical Excellence (NICE), an organization primarily involved in guideline development, has published a strategy that provides information for updating and correcting errors. The method is time-specific but incorporates continual surveillance of the literature and dialogue between the organization and the designated group of guideline developers. The study describes their updating process up to and at two years after publication, as well as during the two to four year time period, and specifically at four years post-publication.[6]

The US Preventative Services Task Force (USPSTF) has also addressed the issue of updating.[7] Because of resource limitations, they prioritize which screening and preventive service topics to update, and the order in which updates are conducted. A committee determines updating priorities based on the public health importance of the topic (burden or suffering and expected effectiveness of preventive services to reduce that burden), the potential for a USPSTF recommendation to affect clinical practice (based on existing controversy or the belief that a gap exists between evidence and practice) and the availability of new evidence that has the potential to change prior recommendations.

Definition of Update

To understand the process of "*updating*" within the context of CERs, consideration should be given to the term "update." The general term refers to extending an evidence report up to the present time or to include the latest information.[8] Moher and Tsertsvadze proposed a formal definition of "update" to mean **a discrete event aiming to search for and identify 'new evidence' to incorporate into a previously completed systematic review**.[9] They assert that central to updating is the effort to identify "new evidence," which they describe in the broadest sense, **irrespective of date of publication.** This is taken to mean any evidence not included in the previously completed review, not just new studies published since the last review. We believe this definition is most appropriate given the purpose of CERs. The definition used by the Cochrane Collaboration is in keeping with this definition.[5]

Assessing Whether to Update

Whether a CER needs to be updated depends on many factors, as several reasons may exist for undertaking an update. The most common reason is to include newly published studies or studies that have been updated with information not previously presented, in order to revise the effect estimate. This includes both changes in magnitude and/or direction of an effect estimate. Another reason is to include new interventions, technologies, diagnostic tests or outcomes in order to provide timely information about new developments in a field. For example, a new medication may be approved by the Food & Drug Administration (FDA) for a particular medical condition. Or the passage of time may bring about a new understanding of disease mechanisms that may change the scope of key questions originally asked. Other reasons for updating may be to include delayed publications to minimize impact of time lag bias, to add missing data obtained from authors of the included studies or to improve the methods of the CER to reflect developments in methodology or the area of health (e.g. to present previously unreported

information on specific outcomes or subgroups).[10][Mike: do you also want to add that updating might be done to correct misunderstandings about studies that were included in the original?]

Several signals for when a systematic review requires an update have been proposed. With funding from AHRQ, Shojania and colleagues defined a quantitative signal as a change in statistical significance using a conventional threshold of p=0.05 or a relative change in effect magnitude ≥ 50%.[11] They also defined a qualitative signal as **"a qualitatively different characterization of effectiveness, a new harm sufficient to affect decision-making, a superior alternate therapy, a caveat that affects clinical decision-making, or the expansion of treatment to a new patient group.**" They found a qualitative or quantitative signal for updating for 57% (95% CI: 47% to 67%) of 100 random SRs, at a median time of 5.5 years (95% CI: 4.6-7.6). Twenty-three percent of SRs had signals indicating the need for updating within 2 years, 15% within 1 year, and 7% of SRs had signals for updating that had already occurred at the time of publication.[11] This work suggests the presence of several indicators that likely co-exist to varying degrees, and highlights the potential of signal detection in the updating process. We feel that Shojania's definition of a "qualitative" signal works best for the EHC program, as it is the most broad and flexible. It uses far fewer resources than would be needed to perform the steps needed to calculate a quantitative signal.

Even using the above qualitative signal as a guide, there is insufficient evidence to identify an optimal approach to deciding which CERs should be updated. We suggest using the following steps to determine whether an update is necessary. The method is based on that of the Southern California Evidence-based Practice Center (SCEPC), which in 2008 was tasked by AHRQ with assessing whether various existing CERs were out of date.

Literature search: In the late 1990s, AHRQ asked the SCEPC to determine whether their clinical practice guidelines needed to be updated and how quickly guidelines go out of date. AHRQ's assignment required that, rather than conducting a series of new systematic reviews, the EPC devise a method that could be feasibly applied to a large number of guidelines. Reasoning that any new findings that differed from the previous ones with sufficient magnitude to warrant reconsideration would be published in either a major medical journal or a prestigious journal in the specific subfield, they used what we will refer to as a "focused" literature search. This focused search included five major medical journals: *Journal of the American Medical Association (JAMA)*, *New England Journal of Medicine (NEJM*), *Annals of Internal Medicine*, *British Medical Journal*, and *The Lancet*. It also included at least four specialty journals tailored to each topic, as recommended by content experts.[12] [Mike: were the afore-mentioned searches full text on the journal's websites or just searches of their records in MEDLINE? I suggest that both types of search should be done for this type of rapid screening.] The starting dates for searches were purposely set at one year prior to the ending dates of the original searches to capture any reports not included in the original searches. Of 17 guidelines, new evidence and expert judgment indicated that seven required a major update; six were found to be in need of a minor update; three were judged as still valid; and for one guideline, no conclusion could be reached.[12]

To compare the comprehensiveness and effort required to employ the method just described with that of a typical full-blown literature search, Gartlehner and colleagues (2004) at the University of North Carolina Chapel Hill and RTI employed both a "focused" and a full traditional search to assess the need to update the 1996 USPSTF Guide to Clinical Preventive Services Guidelines. The study found that although the limited search identified fewer eligible

studies than the "traditional approach," Task Force members who were acting as project liaisons rated none of the studies missed as important to assessing the need for an update to the guidelines.[13] Thus, they deemed the revised approach to be an efficient and acceptable method for assessing the need to update a guideline. We suggest using the same "limited" search technique to assess CER obsolescence.[Mike: when searching to see if a Guideline is out of date, does this include looking for recent SRs? This might be an even quicker step for revealing that there is a problem with the guideline than searching for new pivotal studies, because there will be fewer SRs than studies to check. It will highlight problems, but will not give the "all clear". Checking for new/updated SRs might be especially relevant if Cochrane reviews are relevant to the guideline, because these SR are updated and, once the SR has been published, you know exactly where to find its updated version (ie in the same place as the original). It might also be worth exploring the possibility of an alerts system to inform the guidelines producer of changes to Cochrane reviews they have used.]

Food and Drug Administration (FDA) MedWatch and Canadian Health Services Database Searches: Drug warnings are often based on accumulated adverse events reported by consumers or medical providers to the FDA; these case reports are not often submitted for journal publication. Thus, to supplement searches of the peer-reviewed literature we strongly suggest searching the federal Food and Drug Administration database and the Canadian Health Services (CHS) pharmaceutical database, if the CER discusses products or procedures regulated by these agencies.

Expert opinion: Experts in the field are often aware of new developments before they become public. These developments include new controversies, drugs or devices in development, ongoing trials and cohort studies, papers in submission, and anecdotal reports of adverse events.

Thus, the decision to update a CER should also consider expert opinion, including that of the director of the EPC that conducted the original report (or the principle investigator, if it was not the EPC director). The principal investigator should be asked to suggest at least three Technical Expert Panel (TEP) members, peer reviewers, or other experts whom they believe are in a position to comment (for example, those who recently published an editorial on the topic of interest). Each expert should be asked provide an assessment of the need to update the CER The request should contain an introduction, the original CER key questions, the conclusions corresponding to those questions, and any other questions regarding updating. Including a brief table like the one below will simplify the process. Offering a small honorarium and sending the request by Express Mail tends to increase the response rate. (Maglione cite)[Mike: it might also be worth considering identifying someone within the Cochrane Collaboration who might be keeping a watch over the accumulating literature in a topic area. This might be an author of a relevant Cochrane review, or someone in the editorial base of the Cochrane Review Group responsible for the relevant area of health.]

Table 1. Sample Table for Expert Opinion (Excerpt for Key Question 1 from CER#1)

Conclusions from CER Executive Summary	Is this conclusion almost certainly still supported by the evidence	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD?			
Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure. 10 percent to 65 percent of surgical patients still require medications. The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma.	Yes/No	Yes/No If yes, please discuss, provide references	

Making the determination: Again, per Shojania, if any of the above sources lead to **"a qualitatively different characterization of effectiveness, a new harm sufficient to affect decision-making, a superior alternate therapy, a caveat that affects clinical decision-making, or the expansion of treatment to a new patient group**" the process of updating moves from "when to update," which may be based on priorities and resources of AHRQ, to "how to update" by an individual EPC.

Process for Updating CERs

Identifying studies to include in an update

A primary purpose of conducting an update is to identify relevant new evidence. Updates are also an opportunity to incorporate relevant older evidence, as studies may have been missed by the original searches. This could be due to inadequate initial searches, or errors that occurred in

the application of inclusion or exclusion criteria. In some cases, evidence that was previously excluded will need to be re-considered because the update involves an extension of the originally formulated scope of the review (e.g., population, interventions, or outcomes assessed).[9] In addition, updated publications of previously published studies may also provide relevant evidence not previously presented.[Mike: it might be worth mentioning the possibility that you would seek unpublished, updated data from the original researchers?]

In many cases, new studies will already have been identified through the surveillance strategy (described above) to identify CERs in need of an update. However, surveillance strategies are typically not comprehensive or systematic, due to efficiency considerations. Therefore, once a decision has been made to conduct an update, it is important to perform additional searches that adhere to general principles for conducting systematic searches.[14] These include searches of multiple databases and use of supplemental sources such as reference lists and content experts.[15] The original search strategy can frequently be carried over to the update. However, investigators should also use the opportunity to review the search strategy and modify search terms, databases and other sources searched, or other components. For example, use of governmental and non-governmental clinical trials registries has expanded and their inclusion could provide useful information on in-progress or unpublished trials as well as unpublished outcomes.[16, 17] Investigators should also confirm previous decisions regarding exclusion of grey literature, non-English language literature, or other sources of evidence (such as the FDA website).[18, 19]

In order to limit the number of citations to review, one strategy is to limit the start date for update searches. However, delays between publication in journals and indexing in MEDLINE and other electronic databases occur and are variable in duration.[20] We recommend

using a start date at least one year prior to the end date of the original search. Alternatively, searches could be based on the "entry date"(date the publication was added to Medline) rather than the publication year.[21] Another strategy is to conduct update searches without any date restrictions, using the de-duplication function in various reference library software programs to remove old citations. [Mike: if the search strategy is expanded, it will be important to have guidance on whether the revised search should be used only from near to the end-date of the previous searches or whether the whole literature should be searched again with the expanded search.]

Incorporating new evidence

After new evidence has been identified, it must be incorporated into the update. Methods for incorporating new evidence into an update will vary depending on the amount of evidence and its potential impact on estimates and conclusions.[9] However, additional research is needed to determine optimal methods for incorporating new evidence into an update.[10]

One approach is to incorporate the new evidence into the previous review, updating results (i.e. search yield, number of studies, quality assessments, conclusions), as appropriate. This is easiest in rare cases where a relatively small number of new studies are identified that result in only minor changes in the conclusions of the original SR. Alternatively, the new evidence can be summarized in a distinct section of the review (such as a "summary of update results" section). When substantial new evidence is identified, i.e. when many critical new studies have become available, or a marked inconsistency between the new evidence and the older evidence is apparent, updating the results and analyses will be more intricate. Conducting new quantitative analyses could result in more precise estimates of effectiveness and/or more confidence in conclusions.[Mike: do you wish to recommend that, if there is substantial new material, this

might require the CER to be re-done completely, or at least, re-written? Something else to consider is whether the assessment of the new studies will be consistent with the assessment of the existing studies. If not, should all the studies (new and old) be assessed together?]

Cumulative Meta-analysis (CMA)

If the original review included meta-analysis, one option is conducting cumulative meta-analysis (CMA). CMA is a statistical procedure in which the combined effect estimate is sequentially updated by incorporating results from each newly available study.[22-25] It documents trends in a treatment effect over time and provides clinicians and policy-makers with up-to-date information. When done prospectively, it may be useful in identifying the earliest time at which there is sufficient statistical evidence that an intervention is effective or harmful.[23] However functional, CMA can be costly and time consuming, and increase the potential for an inflated rate of type-I error due to repeated hypothesis testing.[26, 27] [Mike: you should also note that CMA are made more complex if some of the existing studies have been updated.]

Using the cumulative slope as an indicator of stability. 'Cumulative slope' was introduced by Mullen et al. (2001) as an indicator of stability of pooled effect sizes in CMA.[28] The authors describe the slope of the regression line fitted over N data points, and k waves are the rate of change in Z effect size corresponding to the addition of each new study. The smaller the magnitude of the slope is, the greater the confidence that the pooled effect size is becoming constant, suggesting decreased need for updating. Although this approach may be limited by its subjectivity and it does not produce a valid estimate of variance for the cumulative slope, some argue it is more objective than the alternative to visual inspection of CMA. This application may help determine when it is most fitting to stop updating, therefore helping to conserve resources.

Retrospective use of the cumulative slope may also uncover differences amongst studies, or to expose conduct of possibly superfluous studies.

Using sequential monitoring boundaries. Pogue and Yusuf proposed the adaptation of sequential monitoring boundaries used in clinical trials, to the conduct of cumulative meta-analyses.[26] Given problems of inflated type-I error with repeated hypothesis testing, the significance levels of the individual hypothesis tests therefore need to be adjusted so that the cumulative overall error rate does not exceed the pre-specified level of statistical significance. The optimal information size (OIS), a measure of the total amount of information estimated for CMA, is deemed similar to the total sample size needed to detect a pre-specified effect size calculated for a single planned trial. Generally speaking, estimation of the OIS and the utilization of monitoring boundaries provide a prospective context in which to examine trends as evidence accumulates. This estimation also serves to evaluate the statistical strength of the evidence of the treatment benefit, or harm by considering the number of patients observed as a proportion of OIS each time an analysis is performed. This is done while also adjusting for multiple testing. The major limitation to this approach is that a large amount of data is required, as is a priori specification of various factors.

Recursive CMA. Recursive CMA is proposed as an extension of conventional CMA.[29, 30] It allows investigators to explore and document the evolution of the pooled treatment effect of meta-analysis in successive information steps as new, updated, corrected, or unpublished data are incorporated into the results. The pooled effect estimate is recalculated at each information step. It is thought useful for evaluating and comparing the impact of updating, publication bias, and publication lag on the pooled treatment effect estimates in meta-analyses of individual patient data versus summary data. Careful scrutiny of unpublished and updated data is suggested in

order to avoid bias, thus this approach becomes tedious[Mike: “tedious” sounds too negative. Do you mean “labour intensive”?] as well as costly.

Changing methods when conducting an update

In addition to incorporating new evidence, an update is an opportunity to perform additional analyses, correct errors, or incorporate new methods.[31] Feedback obtained on the original review can provide useful information regarding whether to perform additional analyses in an update. For example, if an SR is criticized for its use of a fixed effects model, it might be reasonable to conduct sensitivity analyses using both random and fixed effects models (or changing to a random effects model if deemed appropriate) in the update.[Mike: I would not use fixed and random effects as the example here. Perhaps you could use something such as “the way in which it grouped studies for the meta-analyses”.] Methods for grading individual studies and bodies of evidence and for reporting results of SRs also continue to evolve.

In some cases, changing the methods would involve a substantial additional burden. For example, in recent years several new tools have been developed to assess the quality of clinical trials and observational studies. (CITE). Re-reviewing all included studies according to new quality standards will increase the credibility or scientific validity of reviews. We suggest that investigators review the methods used for the original review and determine whether to update the methods on an individual basis.[Mike: this paragraph mixes together several things and seems to flip backwards and forwards on whether re-assessing study quality is a good or bad thing. Also, the last sentence is very general about methods, whereas the paragraph is mainly about quality assessment.]

Reporting results of the update

In order to make updates most useful to readers, it is important to clearly describe the purpose of the update, methods used to conduct it, and the results. Any changes in the protocol for the review (scope and methods) should be explicitly stated and the rationale described. Important elements to focus on include the search strategy (including the start date of searches), the yield of the searches, important characteristics of new evidence (number, type, size, and quality of studies), and main conclusions, including how the results of the update differ from the original review. Evidence that has the most impact on the conclusions of the update should be emphasized and described in detail. We suggest including a summary table like the one below in the executive summary and the conclusions section.[Mike: do you want to recommend that people should be able to read the update in complete isolation from the original SR? For example, would you encourage or discourage them from describing their methods very briefly and referring the reader back to more detail in the original?]

Table 2. Sample summary table for systematic review update

	2001 Report		2009 Update			Conclusion
Comparison	Number of trials	Result	Number of new trials	Total number of trials	Result	
A vs. B	5	-12% (-22%, -3%)	2	7	-14%(-2-%, -5%)	A more effective than B
A vs. C	3	-3% (-8%, 4%)	0	3	-3% (-8%, 4%)	No evidence of difference
A vs. D	2	1 positive, 1 no benefit	2	4	-6% (-10%, -1%)	No evidence of difference
A vs. E	0	n/a	3	3	-4% (-12%, 3%)	No evidence of difference

[Mike: For this example table, you might want to include a line where some of the trials in the 2001 Report have been removed from the 2009 Update to show how this - which is not rare - would be reported.]

In the case of a new drug, new indication, or a new population group, we suggest adding a new section to the report, in the results section. After the updated report has been approved by the sponsor, we suggest submitting to the journal that published the original review.

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