

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.**
- **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, thus compromising health care policy decisions. This could result in wasted resources, provision of redundant or ineffective 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 Cochrane therapeutic reviews were updates, compared to only 2.4% of 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

29 assessed and updated every two years, or a commentary be added to explain why this is done less
30 frequently.⁵ However, updating all SRs based on an a priori time interval could result in
31 inefficient use of resources, as diverse areas in medicine will vary in how frequently they need to
32 be updated. The UK National Institute for Clinical Excellence (NICE), an organization primarily
33 involved in guideline development, has published a strategy that provides information for
34 updating and correcting errors. The method is time-specific but incorporates continual
35 surveillance of the literature and dialogue between the organization and the designated group of
36 guideline developers. The study describes their updating process up to and at two years after
37 publication, as well as at the two to four year time period, and specifically at four years post-
38 publication.⁶

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

47 **Definition of Update**

48 To understand the process of “*updating*” within the context of CERs, consideration should be
49 given to the term “update.” The general term refers to extending an evidence report up to the
50 present time or to include the latest information.⁸ Moher and Tsertsvadze proposed a formal

51 definition of “update” to mean a **discrete event aiming to search for and identify ‘new**
52 **evidence’ to incorporate into a previously completed systematic review.**⁹ They assert that
53 central to updating is the effort to identify “new evidence,” which they describe in the broadest
54 sense, **irrespective of date of publication.** This is taken to mean any evidence not included in
55 the previously completed review, not just new studies published since the last review. We
56 believe this definition is most appropriate given the purpose of CERs. The definition used by the
57 Cochrane Collaboration is in keeping with this definition.⁵

58 **Assessing Whether to Update**

59 Whether a CER needs to be updated depends on many factors, as several reasons may exist
60 for undertaking an update. The most common reason is to include newly published studies or
61 update studies with information not previously presented, in order to revise the effect estimate.
62 This includes both changes in magnitude and/or direction of an effect estimate. Another reason is
63 to include new interventions, technologies, diagnostic tests or outcomes in order to provide
64 timely information about new developments in a field. For example, a new medication may be
65 approved by the Food & Drug Administration (FDA) for a particular medical condition. Or the
66 passage of time may bring about a new understanding of disease mechanisms that may change
67 the scope of key questions originally asked. Other reasons for updating may be to include
68 delayed publications to minimize impact of time lag bias or to add missing data obtained from
69 authors of primary studies.¹⁰

70 Several signals for when a systematic review requires an update have been proposed. With
71 funding from AHRQ, Shojania and colleagues defined a quantitative signal as a change in
72 statistical significance using a conventional threshold of $p=.05$ or a relative change in effect
73 magnitude $\geq 50\%$.¹¹ They also defined a qualitative signal as “**a qualitatively different**

74 **characterization of effectiveness, a new harm sufficient to affect decision-making, a**
75 **superior alternate therapy, a caveat that affects clinical decision-making, or the expansion**
76 **of treatment to a new patient group.”** They found a qualitative or quantitative signal for
77 updating for 57% (95% CI: 47% to 67%) of 100 random SRs, at a median time of 5.5 years (95%
78 CI: 4.6-7.6). Twenty-three percent of SRs had signals indicating the need for updating within 2
79 years, 15% within 1 year, and 7% of SRs had signals for updating that had already occurred at
80 the time of publication.¹¹ This work suggests the presence of several indicators that likely co-
81 exist to varying degrees, and highlights the potential of signal detection in the updating process.
82 We feel that Shojania’s definition of a “qualitative” signal works best for the EHC program, as it
83 is the most broad and flexible. It uses far fewer resources than would be needed to perform the
84 steps needed to calculate a quantitative signal.

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

90 **Literature search:** In the late 1990s, AHRQ asked the SCEPC to determine whether their
91 clinical practice guidelines needed to be updated and how quickly guidelines go out of date.
92 AHRQ’s assignment required that, rather than conducting a series of new systematic reviews, the
93 EPC devise a method that could be feasibly applied to a large number of guidelines. Reasoning
94 that any new findings that differed from the previous ones with sufficient magnitude to warrant
95 reconsideration would be published in either a major medical journal or a prestigious journal in
96 the specific subfield, they used what we will refer to as a “focused” literature search. This

97 focused search included five major medical journals: *Journal of the American Medical*
98 *Association (JAMA)*, *New England Journal of Medicine (NEJM)*, *Annals of Internal Medicine*,
99 *British Medical Journal*, and *The Lancet*. It also included at least four specialty journals tailored
100 to each topic, as recommended by content experts.¹² The starting dates for searches were
101 purposely set at one year prior to the ending dates of the original searches to capture any reports
102 not included in the original searches. Of 17 guidelines, new evidence and expert judgment
103 indicated that seven required a major update; six were found to be in need of a minor update;
104 three were judged as still valid; and for one guideline, no conclusion could be reached.¹²

105 To compare the comprehensiveness and effort required to employ the method just described
106 with that of a typical full-blown literature search, Gartlehner and colleagues (2004) at the
107 University of North Carolina Chapel Hill and RTI employed both a “focused” and a full
108 traditional search to assess the need to update the 1996 USPSTF Guide to Clinical Preventive
109 Services Guidelines. The study found that although the limited search identified fewer eligible
110 studies than the “traditional approach,” Task Force members who were acting as project liaisons
111 rated none of the studies missed as important to assessing the need for an update to the
112 guidelines.¹³ Thus, they deemed the revised approach to be an efficient and acceptable method
113 for assessing the need to update a guideline. We suggest using the same “limited” search
114 technique to assess CER obsolescence.

115 **Food and Drug Administration (FDA) MedWatch and Canadian Health Services**

116 **Database Searches:** Drug warnings are often based on accumulated adverse events reported by
117 consumers or medical providers to the FDA; these case reports are not often submitted for
118 journal publication. Thus, to supplement searches of the peer-reviewed literature we strongly
119 suggest searching the federal Food and Drug Administration database and the Canadian Health

120 Services (CHS) pharmaceutical database, if the CER discusses products or procedures regulated
121 by these agencies.

122 **Expert opinion:** Experts in the field are often aware of new developments before they
123 become public. These developments include new controversies, drugs or devices in development,
124 ongoing trials and cohort studies, papers in submission, and anecdotal reports of adverse events.
125 Thus, the decision to update a CER should also consider expert opinion, including that of the
126 director of the EPC that conducted the original report (or the principle investigator, if it was not
127 the EPC director). The principal investigator should be asked to suggest at least three Technical
128 Expert Panel (TEP) members, peer reviewers, or other experts whom they believe are in a
129 position to comment (for example, those who recently published an editorial on the topic of
130 interest). Each expert should be asked provide an assessment of the need to update the CER
131 The request should contain an introduction, the original CER key questions, the conclusions
132 corresponding to those questions, and any other questions regarding updating. Including a brief
133 table like the one below will simplify the process. Offering a small honorarium and sending the
134 request by Express Mail tends to increase the response rate. (Maglione cite)

135

136 **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	

137
 138 **Making the determination:** Again, per Shojania, if any of the above sources lead to “a
 139 **qualitatively different characterization of effectiveness, a new harm sufficient to affect**
 140 **decision-making, a superior alternate therapy, a caveat that affects clinical decision-**
 141 **making, or the expansion of treatment to a new patient group”** the process of updating
 142 moves from “when to update,” which may be based on priorities and resources of AHRQ, to
 143 “how to update” by an individual EPC.

144 **Process for Updating CERs**

145 **Identifying studies to include in an update**

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

149 the application of inclusion or exclusion criteria. In some cases, evidence that was previously
150 excluded will need to be re-considered because the update involves an extension of the originally
151 formulated scope of the review (e.g., population, interventions, or outcomes assessed).⁹ In
152 addition, updated publications of previously published studies may also provide relevant
153 evidence not previously presented.

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

168 In order to limit the number of citations to review, one strategy is to limit the start date
169 for update searches. However, delays between publication in journals and indexing in
170 MEDLINE and other electronic databases occur and are variable in duration.²⁰ We recommend
171 using a start date at least one year prior to the end date of the original search. Alternatively,

172 searches could be based on the “entry date”(date the publication was added to Medline) rather
173 than the publication year.²¹ Another strategy is to conduct update searches without any date
174 restrictions, using the de-duplication function in various reference library software programs to
175 remove old citations.

176 **Incorporating new evidence**

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

181 One approach is to incorporate the new evidence into the previous review, updating results (i.e.
182 search yield, number of studies, quality assessments, conclusions), as appropriate. This is easiest
183 in rare cases where a relatively small number of new studies are identified that result in only
184 minor changes in the conclusions of the original SR. Alternatively, the new evidence can be
185 summarized in a distinct section of the review (such as a “summary of update results” section).
186 When substantial new evidence is identified, i.e. when many critical new studies have become
187 available, or a marked inconsistency between the new evidence and the older evidence is
188 apparent, updating the results and analyses will be more intricate. Conducting new quantitative
189 analyses could result in more precise estimates of effectiveness and/or more confidence in
190 conclusions.

191 **Cumulative Meta-analysis (CMA)**

192 If the original review included meta-analysis, one option is conducting cumulative meta-
193 analysis (CMA). CMA is a statistical procedure in which the combined effect estimate is
194 sequentially updated by incorporating results from each newly available study.²²⁻²⁵ It documents

195 trends in a treatment effect over time and provides clinicians and policy-makers with up-to-date
196 information. When done prospectively, it may be useful in identifying the earliest time at which
197 there is sufficient statistical evidence that an intervention is effective or harmful.²³ However
198 functional, CMA can be costly and time consuming, and increase the potential for an inflated
199 rate of type-I error due to repeated hypothesis testing.^{26, 27}

200 **Using the cumulative slope as an indicator of stability.** ‘Cumulative slope’ was
201 introduced by Mullen et al. (2001) as an indicator of stability of pooled effect sizes in CMA.²⁸
202 The authors describe the slope of the regression line fitted over N data points, and k waves are
203 the rate of change in Z effect size corresponding to the addition of each new study. The smaller
204 the magnitude of the slope is, the greater the confidence that the pooled effect size is becoming
205 constant, suggesting decreased need for updating. Although this approach may be limited by its
206 subjectivity and it does not produce a valid estimate of variance for the cumulative slope, some
207 argue it is more objective than the alternative to visual inspection of CMA. This application may
208 help determine when it is most fitting to stop updating, therefore helping to conserve resources.
209 Retrospective use of the cumulative slope may also uncover differences amongst studies, or to
210 expose conduct of possibly superfluous studies.

211 **Using sequential monitoring boundaries.** Pogue and Yusuf proposed the adaptation of
212 sequential monitoring boundaries used in clinical trials, to the conduct of cumulative meta-
213 analyses.²⁶ Given problems of inflated type-I error with repeated hypothesis testing, the
214 significance levels of the individual hypothesis tests therefore need to be adjusted so that the
215 cumulative overall error rate does not exceed the pre-specified level of statistical significance.
216 The optimal information size (OIS), a measure of the total amount of information estimated for
217 CMA, is deemed similar to the total sample size needed to detect a pre-specified effect size

218 calculated for a single planned trial. Generally speaking, estimation of the OIS and the utilization
219 of monitoring boundaries provide a prospective context in which to examine trends as evidence
220 accumulates. This estimation also serves to evaluate the statistical strength of the evidence of the
221 treatment benefit, or harm by considering the number of patients observed as a proportion of OIS
222 each time an analysis is performed. This is done while also adjusting for multiple testing. The
223 major limitation to this approach is that a large amount of data is required, as is a priori
224 specification of various factors.

225 **Recursive CMA.** Recursive CMA is proposed as an extension of conventional CMA.^{29,}
226 ³⁰ It allows investigators to explore and document the evolution of the pooled treatment effect of
227 meta-analysis in successive information steps as new, updated, corrected, or unpublished data are
228 incorporated into the results. The pooled effect estimate is recalculated at each information step.
229 It is thought useful for evaluating and comparing the impact of updating, publication bias, and
230 publication lag on the pooled treatment effect estimates in meta-analyses of individual patient
231 data versus summary data. Careful scrutiny of unpublished and updated data is suggested in
232 order to avoid bias, thus this approach becomes tedious as well as costly.

233 **Changing methods when conducting an update**

234 In addition to incorporating new evidence, an update is an opportunity to perform
235 additional analyses, correct errors, or incorporate new methods.³¹ Feedback obtained on the
236 original review can provide useful information regarding whether to perform additional analyses
237 in an update. For example, if an SR is criticized for its use of a fixed effects model, it might be
238 reasonable to conduct sensitivity analyses using both random and fixed effects models (or
239 changing to a random effects model if deemed appropriate) in the update. Methods for grading

240 individual studies and bodies of evidence and for reporting results of SRs also continue to
 241 evolve.

242 In some cases, changing the methods would involve a substantial additional burden. For
 243 example, in recent years several new tools have been developed to assess the quality of clinical
 244 trials and observational studies. (CITE). Re-reviewing all included studies according to new
 245 quality standards will increase the credibility or scientific validity of reviews. We suggest that
 246 investigators review the methods used for the original review and determine whether to update
 247 the methods on an individual basis.

248 **Reporting results of the update**

249 In order to make updates most useful to readers, it is important to clearly describe the
 250 purpose of the update, methods used to conduct it, and the results. Any changes in the protocol
 251 for the review (scope and methods) should be explicitly stated and the rationale described.
 252 Important elements to focus on include the search strategy (including the start date of searches),
 253 the yield of the searches, important characteristics of new evidence (number, type, size, and
 254 quality of studies), and main conclusions, including how the results of the update differ from the
 255 original review. Evidence that has the most impact on the conclusions of the update should be
 256 emphasized and described in detail. We suggest including a summary table like the one below in
 257 the executive summary and the conclusions section.

258 **Table 2. Sample summary table for systematic review update**
 259

Comparison	2001 Report		2009 Update			Conclusion
	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	2	4	-6% (-10%,	No evidence of

		no benefit			-1%)	difference
A vs. E	0	n/a	3	3	-4% (-12%, 3%)	No evidence of difference

260

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

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