

Establishing Recency and Updating Needs for Cochrane Reviews on Selected Complementary Medicine Interventions: Study Protocol

Study participants: Misty Pratt (mipratt@ohri.ca), Brian Hutton (bhutton@ohri.ca), Susan Wieland (lswieland@gmail.com), Nadera Ahmadzai (nahmadzai@ohri.ca), Becky Skidmore (bskidmore@rogers.com), David Moher (dmoher@ohri.ca)

1. Introduction

Previous research evaluating a cohort of published systematic reviews demonstrated that 7% of reviews were out of date by the time of publication, while as many as 23% went out of date within two years of being completed. The utility of systematic review-based evidence depends on their remaining up-to-date. As such, the Cochrane Complementary Medicine Field and the Knowledge Synthesis group at the Ottawa Hospital Research Institute (OHRI) have determined a set of existing reviews of interest for which signal detection work using the Ottawa Method's qualitative/quantitative signal detection approach and some additional considerations will be performed.

The Ottawa method involves identification of qualitative and quantitative signals/triggers indicating the need of updating of a systematic review. The method has been modified to reflect the process of updating Cochrane complementary medicine reviews. A graphical overview of the modified Ottawa method is provided in **Appendix 1** of this protocol. The proposed work will assess potential triggers signifying the need for updating of six past Cochrane Complementary Medicine reviews outlined in this protocol. The conclusion on whether or not each of the reviews is in need of updating to reflect new literature since their date of publication will be made based on the identification of qualitative and quantitative signals. More detailed explanations of the process and methodologies for this work are outlined in this document.

2. Objectives

The proposed work will be performed to assess the currency priority level for updating the following six Cochrane Systematic Reviews based on a modified Ottawa Method's signal detection approach. Topics were identified by experts within the Cochrane Complementary Medicine Field.

- *Glucosamine therapy for treating osteoarthritis*
- *Acupuncture for shoulder pain*
- *Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis*
- *Ginkgo biloba for cognitive impairment and dementia*
- *Light therapy for non-seasonal depression*
- *Mistletoe therapy in oncology*

Prior to beginning assessment of each review, members of the research team will contact the relevant Cochrane Review Group editors to confirm that updating of the review is not currently underway. The team will then extract publication-related information for the review including the authorship team, year of publication, key questions addressed in the review, and authors' conclusions for each of the key questions addressed in the

systematic review. This information will be used when establishing the list of experts to be contacted for each review, as well as for use in the identification of qualitative and quantitative signals in relation to the conclusions of the originally published review.

3. Methodology to Establish The Need for Updates: Modified Ottawa Method

Assessing the need for updating each systematic review listed above will be carried out as a three-step process according to the Ottawa Method. For each of the six reviews to be assessed as noted in Section 2, this process is as follows:

Phase I: Consultation of Review Authors and Clinical Experts in the Field

1. Collect summaries/conclusions provided by the authorship team for each question (or possibly endpoint) within each review; this summary will be shared with consulting experts when seeking their input regarding the findings (Phase I), as well as when establishing the presence of updating triggers (Phase II.)
2. Develop a matrix of the review's key conclusions to be sent to the participating experts. This matrix will be used to question each expert about the review's conclusions in terms of:
 - a. Whether the conclusion is still valid in their own opinion (*to be answered as yes/no/don't know*);
 - b. Whether he/she is aware of new evidence published since the publication date of the review being assessed (with details if yes);
 - c. Any additional information or perspectives to be shared.
3. Contact the chosen experts for the review, inviting them to participate in this signal detection project. We will work to identify experts best suited for each review, starting with the lead authors on both the original review and included studies. We will discuss other possible experts to contact with NCCAM. These responses will serve as the main approach to develop awareness of important new information which may signal a possible trigger for review updating, including (but not limited to):
 - i. New and/or important harms;
 - ii. Important changes short of opposing findings;
 - iii. Opposing findings (contrary to current review findings);
 - iv. New subgroup effects of relevance;
 - v. New superior treatments available which render the intervention assessed in the review to no longer be of clinical relevance.
 - a. If an expert indicates an opinion that one or more conclusions of the review is out of date and/or provides specific evidence they feel is critical to the decision regarding updating, we will verify it by assessing the evidence brought forward by the expert(s.)
 - b. If the answer for all of the above criteria is "Yes" (that the findings are still valid, in the opinion of the expert) or "don't know," we will consider running a targeted search to assess whether any new evidence has been published.

Experts will be given 10 business days to respond. Two reminders will be sent. A conflict of interest disclosure statement will also be sent to all experts that will be contacted. They will be requested to sign the form and return it along with their replies. The survey will be kept open until a minimum of two clinical experts have responded.

Phase II:

Assessment of Signals for Updating from the New Evidence

Once primary data are identified from the newly identified relevant evidence proposed by responders during Phase 1, the Ottawa method’s qualitative signals assessment will be applied to each new study in relation to the original systematic review’s conclusions to assess whether a signal is suggestive of a need for updating. The process will be as follows:

1. Assessment of the screened/eligible new evidence for qualitative signals will be performed by examining the screened evidence characteristics, reported endpoints and treatment effect estimates in respect to the original review conclusions.
2. Listing the key questions/clinical endpoints more likely in need of updating [signal(s) met for the recommendation(s) of interest]
3. Listing the review conclusions less likely in need of updating (a signal is not met for the recommendation(s) of interest)
4. Compiling all gathered evidence and concluding if the systematic review requires updating. If a qualitative or quantitative signal is not identified, this would indicate that the recommendation may not be in need of updating at the time of this assessment.

What Constitutes a Qualitative Signal?

The table below provides an overview of different signals which can be identified from new literature; additional details regarding these criteria are provided in Figure 1. Newly identified relevant literature will be considered and assessed in light of these considerations which can influence the degree of need for updating of the review in question.

Figure 1: Criteria for Determining a Conclusion is Out of Date

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 meta-analysis or non-pivotal trial
Quantitative criteria signals of changes in evidence	
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent

Potentially invalidating change in evidence:

This category of signal refers to a situation in which it is expected that clinicians do not act upon the results of the original systematic review. Criteria for potentially invalidating change in evidence that might cause such a situation (A1-A3) are presented in Figure 1. All three criteria specify findings from a pivotal trial¹, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- ***Opposing findings from a new study.*** A study has characterized the benefits of the treatment of interest as opposite compared to the original systematic review; for example, definitely effective vs. ineffective; ineffective vs. effective, and vice versa.
- ***Substantial harm in a new study.*** A study has questioned the use of the treatment on the basis of harm, particularly, the treatment would no longer be recommended because the risk outweighs the benefits.
- ***Superior new treatment.*** A new study has presented another treatment that is significantly superior compared to the one assessed in the original meta-analysis (based on efficacy or harm) to the point that it would be preferred in most settings over the intervention in the current review.

Major change in evidence

A major change in evidence refers to situations in which the original systematic review is not suspended or overturned; however, there is a clear potential for the new evidence to affect the clinical decision making. Four specific criteria are presented in Figure 1 (A4-A7), the first three of which specify findings from a pivotal trial, new meta-analysis, more recent practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- ***Important changes in effectiveness short of “opposing findings”.*** A new study presents benefits in different terms (e.g. therapy in the original SR described as “promising”, “likely beneficial” or similar characterization vs. now described as “definitely beneficial”) but does not contradict the original review. In this document, phrases such as “may be effective”, “promising”, trends towards effectiveness” and other such concepts will be categorized as “possibly effective”.
- ***Clinically important expansion of treatment.*** New studies have shown expansion of the role of the treatment; for example, it is now demonstrated that the treatment is beneficial in children or elderly; or the benefit applies not only to secondary prevention but also to primary prevention of the condition of interest.
- ***Clinically important caveat.*** New studies have added an important caveat: 1) about the patient population who benefit, 2) the manner in which treatment has to be delivered in order to derive benefit, 3) sustainability of benefit (e.g. benefit on short term outcomes but not long term ones), or 4) increases in harm that are not

¹ A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Annals of Intern Med, BMJ, JAMA, Lancet, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

- sufficient to undermine use altogether; however, would clearly affect the decision to recommend treatment for at least some patient populations.
- ***Opposing findings from discordant meta-analysis or non-pivotal trial:*** In these criteria, the source is not a pivotal trial, new meta-analysis, more recent practice guideline or recent textbook. Instead, it will be a “discordant meta- analysis”, or trial indexed in ACP Journal Club.

Quantitative Signals of Changes in Evidence

Quantitative signals (items B1, B2) will be assessed, where feasible, by conducting meta-analyses adding new study data to the existing evidence base and analyses from the original review to establish their overall impact (and potential changes) on summary estimates of treatment effect. Cochrane Review Manager software will be used for all meta-analyses performed.

In this context, signals for a need to update the original review will be considered present if:

- A change in statistical significance in the summary effect estimate is observed (e.g. from significant to non-significant or vice versa);
- A change in the magnitude of the summary treatment effect size of 50% or more is identified.

Assessment of original review’s search strategy

In addition to assessing qualitative and quantitative signals using the approach outlined above, an information specialist will provide an assessment of the completeness of each original review’s search strategy in order to help ensure all eligible studies are identified. These assessments will be help to inform the Cochrane Review Group’s future updating searches of the literature.

Safety Alerts

In addition to assessment of experts’ opinions and assessment of new evidence from the literature, the team will also review safety alerts from key sources (e.g. MedWatch, US FDA Safety Information and Adverse Event reporting; UK’s Medicines and Health Care Products Regulatory Agency (MHRA); Health Canada) to monitor for other safety information which may identify an important need to update the reviews being assessed.

Synthesizing Phases I-II:

Phases I-II described above will provide a comprehensive amount of information to assess whether each of the six systematic reviews identified for assessment are in need of updating. Updating need will be categorized as low, moderate or high based on all of this information. While there is a need for some subjectivity in how all of the different criteria are considered collectively and in totality, driving factors for this classification will be based upon the experts’ input and the degree of strength of the new information found, as well as the quantity of key questions/conclusions from each review that may be impacted. The potential impact of new data on choices in clinical practice will also be weighed heavily in this exercise.

4. Deliverables for Each Assessment

Once each assessment is complete, a short report summarizing the process and findings will be prepared. The reports for each of the six systematic reviews to be assessed in this signal detection work will contain the following sections:

1. **Cover page and table of contents**
2. **Introduction with brief summary of the original review findings**
3. **Methods for updating assessment (i.e. in general the methods from above)**
4. **Results from the assessment:** This will entail brief description of the condition and recommendation of interest taken from the original review, perspectives from the experts that were consulted, new finding(s), the specific qualitative signal(s) met (i.e. the types of qualitative and/or quantitative signals identified), references for the new evidence for each specific recommendation, and an assessment of the original review's search strategy
5. **Conclusion:** This will list the recommendation status as to whether the review is in need of updating or not. Priority levels will also be an objective to give a sense how vital the need for an update might be with regard to potential impact on the review's findings (in consideration of possible changes in clinical practice).
 - a. The presence of a signal(s) would indicate the **need for updating of any given recommendation/condition.**
 - b. The absence of any signal(s) would indicate **no need for updating of any given recommendation/condition.**

We will also compile data related to the survey of experts across reviews. If judged of relevance to the members of the research team, a manuscript related to the experiences of identifying clinical expertise for this updating process will be prepared describing obstacles and strategies taken to overcome them, which may be of value to others for future updating of systematic reviews.

Preliminary Listing of Team Members:

- Misty Pratt (Research Assistant)
- Nadera Ahmadzai (Research Associate)
- Becky Skidmore (Information Specialist)
- Susan Wieland (Cochrane Complementary Medicine Field representation)
- Roxanne Ward (Program Manager)
- David Moher (Scientist)
- Brian Hutton (Scientist)

Appendix 1: Overview of the Modified Ottawa Method

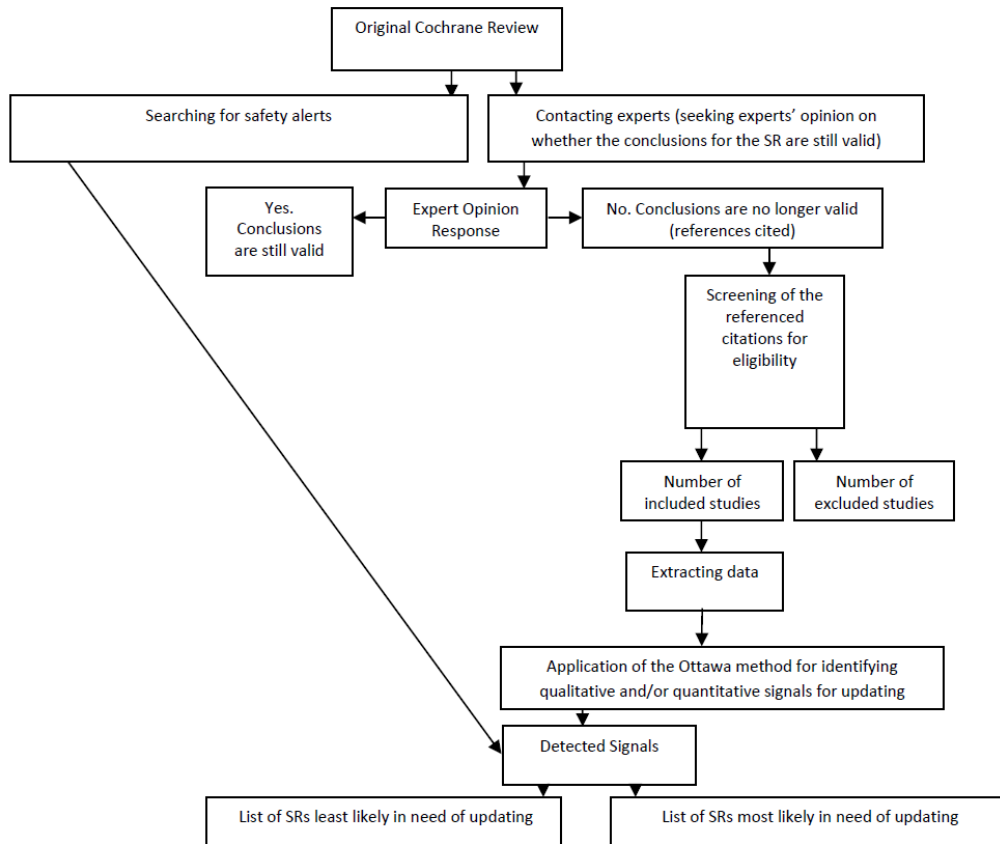


Figure 1: The process of signal detection methods for Cochrane reviews