

Methods Symposium: Advanced Methods and Innovative Technologies for Evidence Synthesis

Session Three: Synthesizing Harms of Interventions

March 8, 2021

Questions and Answers

1. To what extent are harms included in core outcome sets for different areas of health?

Answer: I suspect there's a lot of heterogeneity. Harms are often included as a domain rather than as specific harms outcomes of interest. Also, core outcome sets tend to focus on health problems rather than on interventions. Because harms of drugs might affect anybody who uses the drug, regardless of the health problem for which they take the drug, it might be appropriate to think about core outcomes for harms a little differently.

2. My colleagues and I are currently performing a systematic review on adverse events of iron and erythropoietin administration for preoperative anemia. We have submitted it but notice little willingness to publish this type of results, as they are often not clear cut or precise in nature. How can we promote the publication of this type of reviews, as we are convinced of the importance thereof?

Answer: Great question. Have you considered doing this as a Cochrane review?

3. How do you identify non-public adverse events (AE) sources?

Answer: The ones we used in the **(M)ultiple (D)ata (S)ource** (MUDS) study became public during litigation, but there are other ways to request data and study reports such as Vivli. We have a short guide on ways to access clinical trial data here: <https://restoringtrials.org/accessing-trial-data/>

4. In a study on orlistat we found that only "treatment emergent adverse events" (TEAEs) were reported. TEAE was defined as a new condition or worsening of an existing condition after initiation of the intervention which at first glance seems to make sense. However, worsening or even whether something is "new" is a matter of definition. It depends on what level on the MedDRA hierarchy you are comparing. Many drug trials will have a run-in period from a few weeks up half a year where "baseline" adverse events are gathered which will greatly affect the number of events being reported.

Answer: I agree. Studies with active run-in (sometimes called "enrichment studies") answer questions that are different from trials with no run-in. They're answering conditional questions ("For people who can tolerate the drug...") which are not the same as questions about initiating treatment ("For people starting the drug...").

5. Can you say anything about patient level insight on the importance of level of reporting and non-systematic harms reporting?

Answer: Harms are extremely important to patients. When they know what harms to expect, and they know what matters to patients, trialists could collect information systematically and calculate better

estimates of their likelihood. But as Riaz explained, I think there's also a role for collecting harms non-systematically to capture unexpected harms.

6. Instead of saying that we should not include harms in systematic reviews, I would suggest that we promote the transparent reporting of adverse events? For our review, we have contacted numerous authors and trial investigators, and most of them were not really enthusiastic about sharing data. I think that's a big issue.

Answer: I certainly agree that we should have better reporting and greater transparency in trials, and I agree we should do reviews about harms. I don't think we should include misleading syntheses about harms in reviews that are really designed to assess benefits, which is too often the case.

7. Is there a way of using a more common-sense approach to define "clinically significant harms" that are less reliant on statistical calculations?

Answer: For systematic harms, we could use methods that are like methods used for benefits (e.g., prespecify thresholds for interpretation). There are some systems that include information about the level or severity of events, but analyzing non-systematic events is very difficult.

8. Beyond the risk of bias (RoB), what is the disservice that may occur by systematically reviewing harms? What's the alternative?

Answer: I think the main danger is that we might be giving recommendations that are wrong. An alternative, as Riaz suggested, would be to do reviews focused on harms and using appropriate methods to identify and synthesize that information. Our current approach is often tokenism, which is not a service to patients and providers.

9. Dr. Mayo-Wilson, what is being done now to improve the consistency and openness of harms reporting by clinical trialists?

Answer: Many things. For example, there are now registration and reporting requirements for many trials. But in the US, we only require results reporting on ClinicalTrials.gov for harms above a relatively high threshold (5%).

10. How do we educate (frequently volunteer) peer reviewers and journal editors on how to look at how harms have been described, assessed, and analyzed?

Answer: This is a million-dollar question and I am not sure that I have an easy answer, but it is something that needs to be discussed in the evidence synthesis community.

11. To what extent is the problem at hand even worse than we know because patients may be unlikely to ascribe felt harms to a particular intervention/ medication considering harms are so rarely described in advance to patients receiving a medication?

Answer: This is a great point and I think it is very likely. We can only work with what we have and very often, for harms, what we have is largely incomplete. I think this really speaks to the importance of acknowledging the limitations and not being too confident in conclusions in reviews. Too often you see sweeping generalizations in conclusions like "it is safe" because they didn't find many adverse effects in their included trials. But just because something isn't reported doesn't mean it didn't happen.

12. I'm really interested in Riaz Qureshi's great slide on possible sources of evidence when you're searching for harms info. I'll note two things. First, TOXLINE and TOXNET no longer exist (although you can still search the toxline subset in PubMed with the query tox[sb]). Second, when I first heard about FAERS I thought, "why haven't I been searching this all the time?" and

then I read news coverage like <https://www.statnews.com/2017/06/06/sentinel-fda-drug-risks/> pointing out that FDA Adverse Event Reporting System (FAERS) and indeed Sentinel are incomplete; of course, no one source is ever *complete* but the effort to learn how to search it didn't seem worth it when it sounds like there's a lot missing.

Answer: Yes, sadly TOXLINE and TOXNET no longer exist. I have searched FAERS and afraid I agree it is hard work. I prefer searching Medicines and Healthcare products Regulatory Agency (MHRA) but I think there is currently little evidence on the value of searching these types of sources and whether we should be searching them routinely.

13. Would it be useful for systematic review authors to perform a separate analysis (subgroup or sensitivity analysis) according to how adverse effect data was collected in primary studies (systematically vs non-systematically)?

Answer: Systematic harms could be analyzed much like benefits. For example, the ways in which we analyze and report the outcome “weight” might be the same whether we’re interested in weight as a benefit (e.g., as in a study about diet and exercise) or weight as a harm (e.g., as in a study about antipsychotics). In my opinion, non-systematically assessed harms should probably be analyzed and synthesized separately, but I think there’s a need for more work in this area.

14. I understand the many challenges when incorporating harms in reviews, but shouldn't at least basic information be included (however flawed and with GRADE's very low certainty of the evidence) than not including them in reviews at all?

Answer: It is a good question and I think it is honestly something that the evidence synthesis community needs to consider. If reviewers include some assessment of harms as a token and the validity is questionable, is it worth the effort? Perhaps. Perhaps there is still importance to include something and acknowledge that the certainty of evidence for those harms results will (very nearly always) be very low. But maybe there is an opportunity instead to publish reviews in tandem and focus entirely separate reviews on the different types of questions.

15. Can systematically assessed harms be reported according to selection criteria? Particularly in clinical trial registries, are they reported according to the referred threshold even if they are indicated as systematically assessed?

Answer: “Selection criteria” refer to events. The problems associated with underreporting and cherry-picking harms results are very similar to reporting bias for benefits. Here’s one example:

<https://www.sciencedirect.com/science/article/pii/S0895435618311077>

16. Do you think it is possible to combine different sources of evidence such as publications and clinical trial registries, given the heterogeneity of data reporting, or is it better to choose just one source of evidence in order to tackle this limitation?

Answer: I’d typically use multiple data sources. More about that here:

<https://onlinelibrary.wiley.com/doi/full/10.1002/jrsm.1277>

17. Another explanation could be that patients that experience adverse events will discontinue and will therefore no longer be part of the observational study.

Answer: Yes, observational studies usually are based on current exposures and don't attempt to mimic an intention-to-treat analysis in randomized trials (though it can be done). This can impact reporting and assessment of harms.

18. I am wondering about if you go down the route to include harms in a systematic review (possibly by a hybrid method) but you do not go “all the way” in getting access to data about possible harms (the most common way I guess). How could this shortcoming be reflected in the GRADE assessment?

Answer: Great question. GRADE does a great deal to try and weigh the overall "certainty" of the evidence for a given outcome. While a full discussion wouldn't be feasible to fit in the summary of findings table, in consideration of the different aspects of grade for downgrading the evidence (and potentially upgrading), I think most reviews would be likely finding very low certainty for "harms". Whether specific harms should be included as separate outcomes in the GRADE process is also a consideration and something that I don't think has an answer just yet. It may be worthwhile to explore how reviews that evaluate harms GRADE their harms assessment and then whether those gradings tend to be appropriate or not.

19. It'd be interesting to learn about the most suitable visualization methods to present harms information to patients.

Answer: Agree, to date I've spoken to trialists, statisticians, journal editors and clinical researchers but patients are on the list.

20. Can these plots (volcano and dot plot) be used in systematic reviews and meta-analyses? if yes, do you have any examples?

Answer: Yes, if there are multiple harms in the review then these tools could be utilized; I've not seen it in practice, but we are hoping to include something in an ongoing review.

21. Thank you, Rachel, what is your take on albatross plots to present harms data?

Answer: I believe that could be used in systematic review settings - my research to date has focused on individual RCTs so I've not looked at in detail.

Resources:

Installing Volcano:

ssc install aeovolcano or <https://ideas.repec.org/c/boc/bocode/s458736.html#download>

ssc install aedot or <https://ideas.repec.org/c/boc/bocode/s458735.html>

Extract from Cochrane Handbook re observational studies: 19.1.2.3 Different study designs to measure adverse events section-19-1-2-3:

Some adverse effects occur rarely or may only become apparent long after the start of intervention. This contrasts with adverse effects that have a higher incidence and occur soon after the intervention is delivered. A small randomized trial with only short-term follow-up may be able to capture common, immediately apparent adverse effects (e.g. skin reaction after injection) adequately. However, rare or long-term adverse effects may only be observed in non-randomized studies such as large cohort studies or case-control studies. Therefore, depending on the type of adverse outcome of interest, review authors may need to consider evidence extending beyond the time frame of randomized trials.

Cochrane Handbook for Systematic Reviews of Interventions: <https://training.cochrane.org/handbook>