Reviewer's report

Title: LOST to follow-up Information in Trials (LOST-IT): a protocol on the potential impact

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Reviewer: Andrew Vickers

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I have previously written several methodologic reviews and do believe that they are valuable. I have some concerns about this proposal, however.

In a general sense, the protocol left a bit of a bad taste in my mouth: it felt a little snarky and superior, and I could almost feel the investigators chomping at the bit to publish a paper on just how badly trials were reported and conducted, even in the very best journals. Perhaps this started from the title, which really sets the tone. “Lost it” has a negative connotation, and I could almost hear the methodologists thinking, “those trialists have really lost it”.

Something else that contribute to what I felt was a rather inappropriate tone was the review of previous studies on missing data. The authors seemed to be saying: “gosh, there is a lot of missing data (who’d of thought it?) and investigators don’t do much about it”. I think that the previous studies were a little silly. It makes no sense whatsoever to give an estimate of the proportion of studies with missing data because, in my view, a study is either going to have missing data or not, and there isn’t much you can do about it. A study looking at overall survival will not have missing data, neither should, say, a trial in migraine headache assessing the immediate effect of an analgesic. Any longer term study with patient-reported outcomes will have missing data and you can’t avoid it (I say this as someone who has published research on how to reduce missing data: yes, you can reduce rates of missing data, you can’t eliminate missing data). An estimate of the number of studies with missing data simply reflects the type of studies in the sample.

Second, the complaint that only one in 4 trials adjusted for missing data is misplaced. I have published numerous randomized trials with missing data, but have only adjusted for missing data occasionally. This was sometimes because studies had obviously negative results and other times because the rates of missing data were pretty low.

How will the authors deal with the fact that both the proportion of studies with missing data, and the proportion that corrected for missing data, are essentially uninformative statistics that reflect the types of study in their sample and their results?
On a more methodologic note, I think the investigators are painting themselves into a corner. They are only looking at binary endpoints so they can do some simple imputations (about which, see below). But perhaps the most interesting areas of missing data concern patient-reported outcomes, and this are often continuous (e.g. pain, depression). I see no reason to exclude these studies from the descriptive analysis (e.g. proportion of trials that discussed implications of loss to follow up) just because there are not susceptible to some additional analyses.

On which point, the imputations suggested by the authors are mainly just silly. Assuming that all patients lost to follow-up had the event, or didn’t have the event, or had the event in one group and didn’t in the other, is extremely unsophisticated and well outside accepted practice in missing data analysis. As a simple example, imagine that there was a trial with 500 patients per group, follow-up data on 480 in each group, and 25 and 10 events in control and treatment respectively (5 vs 2%, p<0.01). On what possible grounds would it be realistic to say that the event rate in those lost to follow-up was 50 fold higher than those analyzed?

The normal method of adjusting for loss to follow-up is to build regression models. For example, imagine that in the hypothetical study, the event rate in older patients was 8% and in younger patients 0.5%. One could use the distribution of ages in the patients lost to follow-up to make some guess about likely event rates. Multiple imputation takes this type of method a step further by using a simulation approach. The point is, it is not possible to use these methods on summary data, you need the raw data.

Some other thoughts, problems:

1. There are surely some cases where there are missing data, these are unlikely to influence the results of the trial, and the authors ignore these (e.g. a small amount of missing data in an unambiguously negative trial). Do the authors of the review really want to count such trials as a “problem” (no account taken of missing data)?

2. On page 19: how is “appropriate” and “inappropriate” post-randomization exclusion defined?

3. On page 10, the comments about survival analysis are misplaced. The 2 x 2 table would indeed give you a risk, however, the confidence intervals could not be calculated from the 2 x 2 table.

4. The start of the article is very odd, starting with a “note” about a definition.

5. Table 1 is misformatted

6. Page 21: how is “type of intervention” categorized?
7. Page 18: Loss to follow-up is a strange concept in a survival study, “censoring” occurs because some patients are followed longer than others. However, throughout the protocol, it is as though a patient not followed through, say, 5 years, would be counted as “lost to follow up”.