

Missing outcomes in randomised trials: addressing the dilemma

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After several decades of randomised trials, some aspects of their analysis remain contentious. Two such issues are what to do about trial participants who did not adhere to the protocol, for example if they did not receive the intended treatment, and how to deal with those who did not have outcome assessments, for example because they are lost to follow up. Both of these issues are relevant when adopting a so-called “intention to treat” (ITT) analysis, a topic which not surprisingly also causes debate.

ITT analysis is widely recommended as the preferred method to analyse randomised trials.^{1;2} In an ITT analysis, all randomised patients are included in the analysis in their assigned groups, regardless of any other considerations, including whether they in fact received the designated intervention. ITT analysis should therefore compare outcomes in groups that correspond exactly to the randomisation scheme. Any deviation from that principle may introduce bias.

An immediate problem is that almost all randomised trials have some missing observations.³ Clearly just a few missing outcomes will not be a concern, but one review found that about half of trials have missing outcomes for greater than 10% of randomised patients.⁴ A major concern is that being lost to follow up is related to a patient’s response to the treatment; indeed we should assume that this will be so. That concern can be compounded if the reasons for or frequency of dropout differ between the treatment groups.

No analysis option is ideal here; there is in effect a choice between omitting participants without final outcome data or estimating (imputing) the missing outcome data. What should researchers do? A “complete case” (or “available case”) analysis simply omits those who do not have complete data. This common approach will lose power, and bias may well be introduced as missingness will not be random. Further, excluding some patients is not compatible with the ITT principle. Imputation of the missing data allows the analysis to conform to ITT but requires strong assumptions, which may be hard to justify.^{5;6} However, some concerns about “making up the data” are misplaced.⁷

Methods for imputation of missing values have been the topic of much methodological and empirical research in recent years. The generally preferred imputation methods are quite

complex,⁵⁻⁸ and some simple approaches that have been around a long time are much more popular. One of the simplest and most commonly used for continuous outcomes is “last observation carried forward” (LOCF), in which missing final values of the outcome variable are replaced by the last known value before the participant was lost to follow up. LOCF appeals through its simplicity and ease of application, but there are strong grounds for not using it. Specifically, the method may introduce bias to the results, which can be in either direction according to circumstances.⁹ Also, with LOCF no allowance is made for the uncertainty of imputation so that the resulting confidence intervals are too narrow.¹⁰

Even if missing outcomes are random across trial participants, LOCF assumes that the missing final values would be the same as the last recorded values. That assumption is often implausible (even as an average) because dropping out is likely to be associated with response to treatment – obvious examples are failure to respond to treatment and adverse effects. In practice missing data are very likely to be related to response to treatment and prognosis.

Molnar and colleagues have discussed these issues in the specific context of trials of dementia therapies.^{9;11} They found that 34 of 57 RCTs used LOCF as the only form of ITT analysis. Not surprisingly, that is much higher proportion than the 19% observed in a review of trials across various medical specialties published in four general medical journals.⁴

As Molnar and colleagues note,¹¹ their study cannot quantify the magnitude of the effect of the use of LOCF analysis on trial results, but it highlights the high prevalence of conditions promoting bias in favour of more toxic therapies and against less toxic alternatives.

Their study focussed on a limited number of trials in a single medical condition, but many of the issues apply to all trials. It is known that most trials have some patients whose outcomes are not known, for which an ITT analysis is not possible without some type of imputation (although authors commonly mislabel available case analyses as ITT^{12;13}).

Whichever imputation approach is used it is desirable to report analyses with and without imputation. Also, it may be valuable to explore different imputation approaches. As Molnar and colleagues suggest, “the onus is on the investigators who publish these trials to disprove the possibility that these analyses have introduced bias by performing ITT sensitivity analyses ... particularly for those studies demonstrating higher dropout rates in treatment groups.”¹¹

A further important issue is that information should be included in the report of trial. The CONSORT Statement recommends that authors specify the methods used for all statistical analyses reported.¹⁴ The accompanying explanatory paper included various comments on ITT analysis, but there was no specific mention of imputation.¹⁵ Noting that omission, Shapiro wrote: “A variety of options are available to handle missing data from participants

who drop out of the trial and it is important for readers to know what strategy the investigators adopted. Without such information, the fact that an intent-to-treat analysis was carried out is only partially informative.”¹⁶ That omission will be remedied in the forthcoming 2009 update of the CONSORT Statement.

Transparency of publications facilitates reliable appraisal of quality and relevance.¹⁷ Successful transparency may be judged by the ability for others to reproduce all the methods used. The International Committee of Medical Journal Editors make the sensible recommendation to “Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results”. [<http://www.icmje.org/>] That is very sound advice for all research articles, not just RCTs; indeed I see no reason why it should not apply to all study methods.

Molnar and colleagues have gone further than Shapiro and suggested that CONSORT Group should give guidance on methods for analysing trials when there are missing data.¹¹ CONSORT is about reporting what was done, not advising on what is good or bad methodology, so such guidance will not come from that source. But many others have warned about the dangers of LOCF analysis that its use as the sole form of analysis should surely be discontinued.^{8;9;16;18;19}

Finally, as Liu et al observed, it is important to try to avoid missing data when designing and conducting studies and to try to minimize the bias caused by the inevitable missing data.²⁰ To that end they provided helpful guidance for both the conduct and reporting of RCTs where missing outcomes are likely:

- discuss at the planning stage methods and procedures that maximize the chance of retaining patients (e.g., short course of rescue medicine),
- continue to collect data post-withdrawal to preserve the ITT population,
- document the reasons for missing data,
- anticipate and investigate the types of missing data
- pre-specify primary as well as sensitivity statistical analyses,
- fully report the extent and pattern of missing data
- support conclusions based on results from the planned analyses with proper sensitivity assessment.

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