Little loss to follow-up

From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

2.1f Consider whether outcomes were assessed in all (or nearly all) the people being compared.

Explanation

People in treatment comparisons who are not followed up to the end of the study may have worse outcomes than those who completed follow-up. For example, they may have dropped out because the treatment was not working or because of side effects. If those people are excluded from the comparison, the findings of the study may be misleading.

For example, in a randomized trial of hip protectors for preventing hip fracture, about 20% of participants were lost to follow-up *[Dumville 2006 (RS)]*. The authors dealt with this problem for the main outcome (hip fracture) by accessing the general practice records of patients who were lost to follow-up. However, for other outcomes, such as quality of life, the necessary information had not been recorded, so this was not possible. Therefore, effect estimates for those outcomes could be misleading. Slightly more participants were lost to follow-up in the group assigned to use hip protectors than in the group assigned not to use hip protectors (28% versus 22%). This difference increased the likelihood that participants in the comparison groups were no longer similar, even though they were similar at the start of the trial, as would be expected with random allocation (see Concept 2.1a). By looking at the baseline characteristics of study participants, one can see, for example, that more volunteers, people with poor or fair health, and people with a previous fracture had been lost from the control group than had been lost from the intervention group. It is possible to adjust for those variables in statistical analyses of the results. However, because differences in attrition are difficult to predict, such analyses are rarely planned. Moreover, adjustment can only be made for variables (potential confounders) that have been measured at baseline. Thus, the apparent effect of hip protectors on quality of life is far less certain than the effect on hip fractures.

Basis for this concept

Loss to follow-up in randomized trials can make the results misleading if the unavailability of data is associated with the likelihood of outcome events. Substantial loss to follow-up can lead to overestimates or underestimates of treatment effects. A systematic review of randomized trials published in the top five medical journals found that plausible assumptions regarding outcomes of patients lost to follow-up could change the interpretation of results of as many as one-third of the included trials *[Akl 2012 (SR)]*.

Several systematic reviews have found that, on average, randomized trials reporting higher levels of attrition (loss to follow-up) were likely to overestimate treatment effects compared to trials with lower levels of attrition *[Armijo-Olivo 2021 (SR), Armijo-Olivo 2020 (SR), Nüesch 2009 (SR)]*. Other systematic reviews have reported underestimation of effects or inconclusive findings about the association between attrition and effect sizes *[Hartling 2014 (SR), Page 2016a (SR), Savović 2012b (SR), Wang 2021 (SR)]*. All these reviews included comparisons between studies and have a high risk of confounding by other characteristics of the studies that were compared. Nonetheless, they are consistent with the logical explanation of how excluding people who were lost to follow-up can be

misleading, and it is likely that the direction and magnitude of bias due to attrition varies *[Nüesch 2009 (SR)]*.

Most randomized trials report the number of participants lost to follow-up, but many do not report analyses that take account of loss to follow-up or assess the robustness of analyses that exclude participants who were lost to follow-up *[Barretto Dos Santos Lopes Batista 2019 (SR), Wood 2004 (SR)]*. The best way to prevent "attrition bias" is through efforts to retain participants in studies *[Gillies 2021 (SR)]*.

Missing data from loss to follow-up can be dealt with statistically by various methods including, for example, imputing values based on assumptions about the missing data to give a conservative estimate of the treatment effect. However, the risk of bias still remains when trials do not collect adequate data to yield accurate estimates *[Hollis 1999 (SR)]*, and even small numbers of participants lost to follow-up can have an impact on the results of treatment comparisons *[Walsh 2015]*.

Implications

Be cautious about relying on the results of treatment comparisons if many people were lost to follow-up, or if there was a big difference between the comparison groups in the proportions of people lost to follow-up.

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