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A systematic survey on reporting and methods for handling missing participant data for continuous outcomes in randomized controlled trials

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Abstract

Objective: To assess analytic approaches randomized controlled trial (RCT) authors use to address missing participant data (MPD) for patient-important continuous outcomes.

Study Design and Setting: We conducted a systematic survey of RCTs published in 2014 in the core clinical journals that reported at least one patient-important outcome analyzed as a continuous variable.

Results: Among 200 studies, 187 (93.5%) trials explicitly reported whether MPD occurred. In the 163 (81.5%) trials that reported the occurrence of MPD, the median and interquartile ranges of the percentage of participants with MPD were 11.4% (2.5%–22.6%).Among the 147 trials in which authors made clear their analytical approach to MPD, the approaches chosen included available data only (109, 67%); mixed-effect models (10, 6.1%); multiple imputation (9, 4.5%); and last observation carried forward (9, 4.5). Of the 163 studies reporting MPD, 16 (9.8%) conducted sensitivity analyses examining the impact of the MPD and (18, 11.1%) discussed the risk of bias associated with MPD.

Conclusion: RCTs reporting continuous outcomes typically have over 10% of participant data missing. Most RCTs failed to use optimal analytic methods, and very few conducted sensitivity analyses addressing the possible impact of MPD or commented on how MPD might influence risk of bias.

Keywords: Missing participant data; Continuous outcome; Analytic approaches; MPD; Randomized controlled trials; Lost to follow-up

1. Introduction

Missing participant data (MPD) in randomized controlled trials (RCTs)—also referred to loss to follow-up, discontinued prematurely, or outcome not assessable [1]—refers

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What is new?

Key findings

- Frequently (over 15%) trials authors did not state the analysis strategy for MPD; less than 10% trials conducted sensitivity analyses examining the impact of MPD.

What this adds to what was known?

- Among the studies that do not use complete case for primary analysis, trialists often used last observation carried forward to deal with MPD, a demonstrably poor analytical approach.

What is the implication and what should change now?

- When deal with missing continuous data in randomized trials, trialists should use optimal analytic strategies and conduct sensitivity analyses to assess the impact of MPD on risk of bias.

to missing information on outcomes of interest [2]. Although analyzing patients in the groups to which they were randomized will avoid bias for patients with complete data [3–5], it does not address bias due to MPD, which, if it is substantial and the reasons for MPD differ between the intervention and control groups, is likely to bias the results. For instance, if patients destined to experience poorer quality of life at study termination withdraw consent more frequently from the intervention group than from the control group, and are excluded from the analysis, the results will be biased in favor of the treatment.

A common classification of the reason for missing data (also called missing mechanism) includes missing completely at random (MCAR), missing at random (MAR), and not missing at random (NMAR) [6]. When outcome data are MCAR, it indicates no systematic differences between missing and observed values implying that including only those with available data (complete case) in the analysis will not bias point estimates but enlarge the standard error. Outcome data MAR denotes an explainable systematic difference between missing and observed values based on observed data. Ignoring missing data may cause bias in this case and imputation or data augmentation methods may reduce the extent of bias.

When outcome data are NMAR, systematic differences between missing and observed values can only be explained by unobserved data (eg, a person not responding to treatment is more likely not to provide an observation) [7]. NMAR requires conducting sensitivity analysis comparing effect estimates under different missing mechanisms [6,8]. Seldom if ever can investigators be confident that their data are MCAR; thus, assuming some degree of MAR or NMAR is likely to be a more appropriate approach.

Despite the fact that investigators often expend enormous effort to prevent MPD, as the previous series (paper 1) mentioned, MPD is frequent in RCTs across all therapeutic areas [9–12].

Researchers have thoroughly investigated how RCT authors have dealt with MPD in studies focusing on dichotomous outcomes [1,12,13]. Dealing with continuous MPD has special challenges [14]. Considering the serious threat of bias from MPD, statisticians and methodologists have developed a variety of methods to deal with MPD in RCTs focusing on continuous outcomes [15–20]. Whether trialists are planning and applying the optimal approaches to handle continuous MPD is unknown.

We therefore conducted a systematic survey of RCTs reporting on continuous outcomes to assess (1) how trial authors report MPD for patient-important continuous outcomes and (2) the analytic approaches they use to address MPD.

2. Methods

2.1. Definitions

We defined MPD as unavailable data from trial participants that, if available, would have been included in the analysis of the specific outcome in RCTs. We defined a patient-important outcome as an outcome for which a patient would say "yes" to the following question: "If this outcome were the only thing to change with treatment, would the patient consider receiving this treatment if it is associated with burden, side effects, or cost?" [13]. We used a taxonomy characterizing a hierarchy of the importance of outcomes to select one outcome of primary interest from each trial (Appendix A at www.jclinepi.com). Patient-important continuous outcomes high on this hierarchy include quality of life, symptoms, and functional status. We did not consider surrogate outcomes as patient-important outcomes.

We defined complete case analysis as excluding all patients with any missing value for the outcome being analyzed [21]. In contrast to the complete case analysis, all available data analyses refer to using all available observations for a particular outcome; this means including data from patients with some missing values for that outcome. All available data analyses are commonly seen in trials with repeated measures [2].

2.2. Eligibility criteria

2.2.1. Inclusion criteria

Eligible studies fulfilled all of the following criteria:

- Published in 2014 in one of 119 core clinical journals;
- Described by authors as an RCT;
- Reported an analysis of data for at least one patient-important outcome analyzed as a continuous variable.

2.2.2. Exclusion criteria

We excluded studies meeting any of the following criteria: