Journal of Clinical Epidemiology 76 (2016) 147−154

Journal of Clinical Epidemiology

Three challenges described for identifying participants with missing data in trials reports, and potential solutions suggested to systematic reviewers

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Accepted 23 February 2016; Published online 2 March 2016

Abstract

Objective: To categorize the challenges in determining the extent of missing participant data in randomized trials and suggest potential solutions for systematic review authors.

Study Design and Setting: During the process of updating a series of Cochrane systematic reviews on the topic of anticoagulation in patients with cancer, we identified challenges and used an iterative approach to improve, and a consensus process to agree on the challenges identified, and to suggest potential ways of dealing with them. The five systematic reviews included 58 trials and 75 meta-analyses for patient-important dichotomous outcomes with 27,037 randomized participants.

Results: We identified three categories of challenges: (1) Although systematic reviewers require information about missing data to be reported by outcome, trialists typically report the information by participant; (2) It is not always clear whether the trialists followed up participants in certain categories (e.g., noncompliers), that is, whether some categories of participants did or did not have missing data; (3) It is not always clear how the trialists dealt with missing data in their analysis (e.g., exclusion from the denominator vs. assumptions made for the numerator). We discuss potential solutions for each one of these challenges and suggest further research work.

Conclusion: Current reporting of missing data is often not explicit and transparent, and although our potential solutions to problems of suboptimal reporting may be helpful, reliable and valid characterization of the extent and nature of missing data remains elusive. Reporting of missing data in trials needs further improvement.

Keywords: Missing participant data; Attrition bias; Non-compliance; Lost to follow-up; Randomized controlled trials; Systematic reviews

1. Introduction

Missing data for the outcomes of study participants—missing participant data (MPD)—is a frequent problem in clinical trials. Studies addressing the frequency of MPD found that 87% of trials report on participants for whom data for the primary outcome were missing [1], with the average percentage of participants of MPD ranging from 6% to 32% [1−3]. Moreover, it was unclear in 19% of trials how MPD was handled in the primary analysis [1].

MPD is not only prevalent, but it represents a serious potential source of bias [4]. Indeed, applying plausible assumptions regarding outcomes of participants with missing data could change the statistical significance of results of many randomized controlled trials (RCTs) published in top medical journals [1].

To assess the risk of bias associated with MPD [5−7], systematic review authors need to, for each outcome, identify which participants actually have missing data. In spite of improvements in trial reporting since 2001 (date of publication

Conflict of interest: None.

Funding: This study was funded by Cochrane Methods Innovation Fund.

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http://dx.doi.org/10.1016/j.jclinepi.2016.02.022
0895-4356/

What is new?

Key findings

- Trialists typically report the information about missing data by participant and not by outcome.
- Trialists do not typically report on whether certain categories of participants (e.g., noncompliers) suffer from missing data or not (i.e., were followed up or not).
- It is not always clear how the trialists dealt with missing data in their analysis.

What this adds to what was known?

- We suggest pragmatic solutions for systematic review authors to deal with different challenges related to identifying and dealing with missing participant data in trial reports.

What is the implication and what should change now?

- There is a need for better reporting of trial with respect to missing participant data, and for validating our suggested solutions.
- There is a need for making raw data from trials publicly available.

of CONSORT statement) [8], reporting of missing data remains suboptimal. Indeed, missing values information is still not present in one quarter of RCT reports and is more poorly reported than other items listed in CONSORT [2].

In previous work related to MPD, we noted the limitations in reporting and identified challenges in abstracting information regarding MPD [1]. Specifically, we found that 13% of trials did not report whether MPD occurred. In those that did report MPD, a fifth did not report on how they handled them [1].

A recent methodological survey assessed the reporting and handling methods of MPD in 190 Cochrane systematic reviews in the mental health field [9]. The survey found that only 8% of the systematic reviews clearly reported that the included trials had no missing outcome data for the primary outcomes. Although more than half of the trials included in the meta-analysis had a dropout rate between 10% and 30%, a clear definition of attrition was missing from 97% of the systematic reviews [9].

During the process of updating a series of Cochrane systematic reviews on the topic of anticoagulation in patients with cancer [10−14], we categorized the challenges with extracting MPD. In this article, we discuss these challenges and suggest potential strategies to deal with them for systematic reviewers.

2. Methods

2.1. Development method

In previous work, we had informally noted challenges to abstracting information regarding MPD [1,15] and developed initial thoughts regarding categorization and possible solutions [15]. In this project, we endeavored to formalize both the categorization and potential solutions. The data abstractors for the five systematic reviews noted the challenges with abstracting MPD data from the included randomized clinical trials and sought potential ways of dealing with them [10−14]. They later discussed those challenges and potential solutions with other members of the team and refined them in an iterative manner. The group agreed on the final version of the challenges and solutions through consensus.

2.2. Focus of the article

The work presented in this article focuses on dichotomous outcome data obtained from randomized clinical trials included in five Cochrane systematic reviews addressing anticoagulation in patients with cancer [10−14]. The five systematic reviews included 58 trials and 75 meta-analyses for patient-important dichotomous outcomes with 27,037 randomized participants. This study relates to trial-level data (i.e., derived from a trial report) and not to participant-level data (i.e., individual participant data). It relates to participants with missing data as opposed to missing studies (e.g., unpublished studies), outcomes (e.g., unreported outcomes), or study-level characteristics (for subgroup or meta-regression analyses). It addresses the challenges and solutions from the perspective of the systematic reviewer and not the trialist. Indeed, although improving trial reporting would prevent many of the challenges, we discuss only solutions that would help the systematic reviewer deal with trials with suboptimal reporting. In addition, the challenges might be less relevant to meta-analyses pooling effect estimates based on survival analysis (e.g., hazard ratios), which would have taken into account, at least to some extent, the issue of MPD.

2.3. Definitions

We distinguish between premature end of follow-up, which is specific to a participant, and MPD, which is specific to an outcome. Premature end of follow-up refers to the cessation of following up of a specific participant before the planned end of study follow-up. MPD refers to the unavailability of data for a specific outcome for a specific participant. Thus, premature end of follow-up could result in MPD for a number of outcomes, but not for (1) outcomes in which an event occurred before the participant being lost to follow-up or (2) outcomes that had shorter follow-up periods than the time that the participant was actually followed.

Fig. 1 graphically depicts individual participant data from a hypothetical example illustrating the relationship between the two concepts when considering a specific