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A systematic review finds variable use of the intention-to-treat principle in musculoskeletal randomized controlled trials with missing data

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Abstract

Objectives: In randomized trials, the primary analysis should be consistent with the intention-to-treat (ITT) principle and should address missing data appropriately to draw valid inferences. This review focuses on current practices relating to the ITT principle and methods to handle missing data in the major musculoskeletal journals.

Study Design and Setting: A systematic review of randomized trials published in 2010 and 2011 in five musculoskeletal journals was performed.

Results: We reviewed 91 trials: 38% performed a full ITT analysis (analyzing outcome data for all randomized participants) and 31% performed a partial ITT analysis (excluding participants with no follow-up data). The overall median dropout was 12%; 60% of trials had more than 10% dropouts, and 32% of trials had more than 20% dropouts. Among those that performed an ITT analysis, the majority adopted a form of single imputation; last observation carried forward was the designated approach in most cases. Mixed models for repeated measures and/or multiple imputations were limited to eight trials.

Conclusion: It appears that many trials reporting missing data are inappropriately analyzed and may therefore be prone to biased estimates and invalid inferences.

Keywords: Randomized controlled trial; Musculoskeletal conditions; Intention-to-treat; Missing data; Dropout; Sensitivity analysis; Systematic review

1. Introduction

Intention-to-treat (ITT) analysis is the preferred method for randomized controlled trials (RCTs) with a superiority design. The ITT principle states that an analysis should include all study participants in the groups to which they were randomized, regardless of any departures from the original assigned group [1]. This principle helps to preserve the benefits of randomization, which is intended to ensure that differences in outcome observed between groups are solely the result of the treatment [2,3], and to reduce the risk of selection bias [4,5]. In an ideal setting, all subjects enrolled in an RCT would follow the study protocol and complete their allocated treatment as detailed therein, thus contributing data that are complete in all respects [6]. However, this is rarely achieved in practice—particularly under pragmatic trial conditions [7]. Moreover, to provide an unbiased estimate of treatment effect, randomization alone is insufficient—it is also important to obtain complete data on all randomized subjects and include these in the analysis [8]. Some authors, however, describe an analysis as ITT without regard to this requirement to include data for all randomized participants in the analysis [9]. We refer to an approach that deviates from a full ITT (FITT) analysis in this way—by retaining treatment group membership as per random allocation but excluding participants with no follow-up data—as a partial ITT (PITT) analysis. (The term ‘‘modified intention-to-treat’’ has frequently been used to describe this approach [9], but this term has been criticized for being ambiguous and lacking clarity regarding the exclusion of data [10,11].)

Because of a perceived misuse of the term ‘‘intention-to-treat’’ [10–12], item 16 in the 2010 CONSORT statement was updated to include a more explicit request for group-wise details on the number of participants included in each analysis and whether the analysis was randomized by groups [12]. Non-ITT analyses such as an ‘‘as-treated’’ (AT) analysis, which groups participants according to treatment received rather than according to randomization, and a ‘‘per-protocol’’ (PP) analysis, which omits participants who do not follow the study protocol, are not protected

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What is new?

Key findings

- In accordance with the intention-to-treat (ITT) principle, most trials analyzed data by the groups to which subjects were randomized regardless of the intervention received. However, many failed to obtain outcome data for all randomized subjects and/or include all subjects in the primary analysis.
- On average, the dropout rate was a little over 10%, and because most trials failed to use appropriate statistical methods to account for missing data, it is likely that descriptive data and inferential estimates of treatment effect were biased, given that missing data probably differ from reported data.

What this adds to what was known?

- Many trials are not carrying out an ITT analysis as recommended by guidelines. The violation of the ITT approach largely concerns inappropriate handling of missing data.
- The present study found sensitivity analyses to be infrequently and inappropriately used and insufficiently reported.
- It appears that only modest progress has been made, subsequent to previous reviews, in reducing the large proportion of trials that are inappropriately analyzed.

What is the implication and what should change now?

- ITT is the gold standard approach to the analysis of randomized clinical trials with hypothesis testing in respect of superiority of treatment. However, deviation from the ITT approach is common, particularly in respect of analysis of incomplete data, which may result in biased estimates and give rise to invalid inferences. Trialists should ensure that missing values are handled judiciously and apply methods of analysis that make appropriate assumptions about the missing data.

by randomization and thus may be affected by imbalance in baseline variables [13].

The basic issue in an analysis of trial data with missing values is the selection of an ITT analysis data set. White et al. [14] stated that a true ITT analysis is possible only when there is no missing outcome data. However, in practice, no matter how well designed and implemented a study, missing data are almost inevitable [15]. Hence, the benefits of randomization may be compromised; any statistical inferences, therefore, rely on additional assumptions. Incomplete outcome data can lead to problems such as loss of efficiency due to reduced sample size and—if data are missing disproportionally in each arm and/or for different reasons—bias in the estimate of treatment effect due to differences between the observed and unobserved data [16]. Therefore, a full data set requires either imputation of missing values or modeling of unobserved data [17]. Any analysis of RCTs with incomplete data is based on specific assumptions on the missing data mechanism, such as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR) [18,19]. Under the MCAR mechanism, missingness is independent of both observed data (eg, baseline covariates and observed responses) and unobserved data (those observations that would have been recorded if the patients had stayed in the study). Under the MAR mechanism, missingness depends on observed data but not on unobserved data. Under the MNAR mechanism, missingness depends on unobserved data.

As trials with missing data may not retain the balance of randomization, the basis for statistical inference is lost [6,20], and there is no longer a statistical rationale to guarantee lack of bias for the estimation of the parameter and its associated confidence interval—even if the study is assumed to be free of other risks of bias, such as nonmasked evaluation. Identification of the underlying missing data mechanism is important to carry out appropriate formal analyses of data with missing values; however, it is impossible to identify this mechanism with certainty based on the observed data alone [21]. Missing data should therefore be considered at the design, conduct, and analysis stages of a trial [14,22,23]. First, trialists should attempt to minimize missing data in the first instance by following up all randomized subjects, even if they withdraw from an allocated intervention. Second, analysts should perform a primary analysis with a plausible assumption on the mechanism of missing data. Third, sensitivity analyses should explore the robustness of the results to a range of alternative plausible assumptions regarding missingness.

A few studies [24–28] have examined practices regarding the use of the ITT principle and/or the reporting and handling of missing data in RCTs published in general medical journals. Additionally, two studies have assessed these issues in RCTs in musculoskeletal conditions [29,30].

These studies found many instances in which analyses were poorly defined and described and noted variation in practice regarding the ITT principle and the handling of missing data. For example, Gravel et al. [27] evaluated 403 reports of RCTs published in 2002 in 10 medical journals and reported that 62% of the trials analyzed their primary outcome on an ITT basis. However, only 39% of trials analyzed all subjects as randomized. The study also reported that 60% of trials had at least some missing data and most of these trials (59%) excluded subjects with missing data from the primary analysis. In the musculoskeletal field, Baron et al. [29] examined the use of the ITT