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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:

- RCT reporting time to event outcomes and analyzing those as continuous data;
- Nonhuman trials;
- Cluster RCT, factorial RCT, crossover RCT, n-of-1 trials, cost–utility studies;
- Studies reporting continuous outcomes but analyzed as dichotomous data;
- Meta-analysis of two or more previously published RCTs;
- Secondary analysis of RCTs.

2.3. Literature search

We conducted the search using the Cochrane Collaboration's highly sensitive search strategy to identify RCTs through Medline (OVID interface) in the 119 core clinical English journals indexed under Abridged Index Medicus by the National Library of Medicine (available at http://www.nlm.nih.gov/bsd/aim.html) (see Appendix B at www.jclinepi.com).

2.4. Random sampling of citations

We retrieved a random sample of the identified citations using generated random numbers from an Excel sheet and retrieved correspondingly citation numbers. We repeatedly sampled and screened identified citations meeting eligibility criteria until we achieved the target sample size.

2.5. Study selection and data collection

A team of 20 reviewers, with health research methodology training, worked in pairs using standardized forms to conduct screening of title and abstract, screening of full text, and data abstraction, all independently and in duplicate. We applied a calibration process before screening and data abstraction to ensure accuracy. For both screening and data abstraction, reviewers resolved disagreement through discussion and with the assistance from an independent arbitrator (Y.Z.) if needed. We also reviewed supplementary documents published by the authors to abstract information on detailed description on the reporting and analysis of MPD. We conducted screening and data abstraction using Web-based systematic review software DistillerSR created by Evidence partners (© 2017 Systematic Review and Literature Review Software from Evidence Partners, https://systematic-review.ca).

2.6. Selection of outcome and comparison

For RCTs including more than one patient-important continuous outcome, we selected the primary outcome as the authors reported. If authors reported more than one primary continuous outcome, we selected the first one reported in the abstract. For RCTs including more than one patient-important continuous outcome with none reported as the primary outcome, we selected the outcome first reported in the abstract, or in the results if not presented in the abstract.

In multiple-arm RCTs, we considered the first comparison reported in the results. For RCTs with multiple follow-up times, we used the analysis that included all time points or, if there was no such analysis, the analysis focused on the longest follow-up time.

2.7. Data abstraction

For each trial, we abstracted data regarding general characteristics, methodological characteristics, reporting, and conducted analytic approach regarding MPD, and the extent of MPD. We recorded the categories trial investigators used to describe participants with potential MPD including ineligible participants, mistakenly randomized, did not receive any intervention, withdrew consent, dead, experienced adverse events, noncompliant or nonadherent, discontinued prematurely, excluded as part of center exclusion, and outcome not assessable. We also recorded the missing mechanism the trial assumed when dealing with MPD, whether authors reported a justification of their approach to MPD, as well as whether trialist assessed risk of bias associated with MPD.

2.8. Sample size

We chose a sample size to achieve a precise confidence interval (± 0.05) around the proportion of RCTs that conducted primary analytical approach regarding MPD. In the most conservative situation in which the proportion is 0.5, we would need 200 RCTs to achieve the desired confidence interval (0.45, 0.55).

2.9. Analysis

We assessed agreement for eligibility between reviewers at both the title and abstract screening stage and the full-text screening using kappa statistics. We followed the interpretation guideline from Landis and Koch [22]: kappa values of 0–0.20 represent slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and greater than 0.80 almost perfect agreement.

For all descriptive analyses, we used absolute number and percentages for dichotomous (categorical) variables and mean with standard deviation for continuous outcomes when distribution was normal or near normal. When the distribution was skewed to a large extent, we used median and interquartile range.

2.9.1. Categories of trial participant investigators considered as having MPD

For all the categories that trial investigators used to describe participants with potential MPD, such as "ineligible participants," "withdrew consent," "outcome not assessable," we reported the number and percentage of trials documenting the categories.

2.9.2. Reporting and extent of MPD

We calculated the percentage of participants with MPD in each trial and the median and interquartile range of the percentage across all trials. For trials with multiple follow-up times, in addition to these analyses, we also calculated:

- The percentage of missing data points overall through the entire follow-up counted as the number of missing data points divided by total number of possible data points.
- At the last follow-up time, the percentage of missing data points counted as the number of missing data points divided by the total number of possible data points.

We planned to conduct a logistic regression in which the dependent variable was whether trials did or did not report MPD and the independent variables were as follows:

- Sample size
- Type of intervention (pharmaceutical vs. surgical/invasive nonsurgical vs. others)
- Type of funding (for profit vs. not for profit vs. no funding reported)
- Journal type (top 5 vs. nontop 5)

Top 5 refers to the five general medical journals with the highest impact factor in 2015: *Annals of Internal Medicine*, *British Medical Journal*, *Journal of the American Medical Association*, *The Lancet*, and *New England Journal of Medicine* (*http://impactfactor.weebly.com/medicine.html*).

- Allocation concealment (inadequate vs. adequate)

Our a priori hypotheses were as follows: trials with smaller sample size, for-profit type of funding, nonpharmaceutical type of intervention, inadequate allocation concealment, and nontop 5 medical journals were less likely to report MPD. We also conducted a linear regression with "the percentage of MPD" as dependent variable and the same independent variables described previously and the same directional hypotheses.

2.9.3. Planning and conduct of analyses addressing MPD

We documented the frequency of planned analysis regarding MPD for all continuous outcomes and the analysis conducted by trial investigators for the chosen outcome. We planned to conduct a logistic regression with whether trials planned a sensitivity analysis regarding MPD as the dependant variable and the independent variables as noted previously. Our a priori hypotheses were as follows: trials with smaller sample size, for-profit type of funding, nonpharmaceutical type of intervention, inadequate allocation concealment, and nontop 5 medical journals would be less likely to plan a sensitivity analysis regarding MPD.

The analysis was performed using the SPSS software, version 22/12 (IBM Corp., TX, USA).

3. Results

3.1. General characteristics of included RCTs

We included 200 eligible trials that met out target sample size (Fig. 1). Agreement between reviewers was substantial: kappa of 0.63 for title and abstract screening and 0.64 for full-text screening.

Table 1 presents the general trial characteristics and Table 2 the methodological characteristics of the eligible studies. Symptoms (84, 42%), quality of life (44, 22%), and functional status (33, 16.5%) were the most frequently investigated continuous patient-important outcomes. All but one trial reported time at which patients were followed up; the median follow-up time was 3.3 months (interquartile range of 0.7–12 months). Of these 199 trials, 92 (46%) reported a single follow-up time and 107 (53.5%) multiple follow-up times.

3.2. Reporting and extent of MPD

Table 3 presents information regarding the reporting of missing participant data. Among the 200 trials, 187 (93.5%) had, in the main text or CONSORT flow diagram, an explicit statement of whether MPD occurred. Among the 187 trials that explicitly reported the presence or absence of MPD, 24 (12%) explicitly stated MPD did not occur, and 163 (81.5%) explicitly reported the extent of MPD, of which 44 (27%) trials reported the percentage of MPD in each arm and overall; the overall median and interquartile range of participants in all time points with MPD were 11.4% (2.5–22.6%). The reporting of MPD was mainly focused on the number of patients who had MPD for the overall study sample but not by the specific outcome.

For 91 trials that included multiple follow-up times and reported MPD from either overall or per arm or both, the median and interquartile range for the percentage of total missing data points were 13.1% (6.1–23.7%). At the last follow-up time, the median and interquartile range for the percentage of missing data points were 14.4% (7.4–23.6%). None of the differences between intervention and control in the frequency of missing data approached conventional levels of statistical significance.

We could not conduct the logistic regression with the dependent variable explicitly reporting (or not) the occurrence of MPD because of the small number of studies (13, 6.5%) that failed to report whether MPD occurred.

We conducted a multiple linear regression addressing the percentage of participants with MPD based on sample size, type of intervention, funding, journal, and allocation concealment. A significant beta coefficient indicated that there was a higher percentage MPD when sample size was larger (beta coefficient 0.01 [0.0–0.02], $P = 0.005$, meaning the MPD would be 1% more for each 100 patients), with an R^2 of 0.17 (Appendix C at www.jclinepi.com). We further explored the correlation between larger sample size and higher percentage of missing data using a bivariate analysis and found a correlation coefficient of

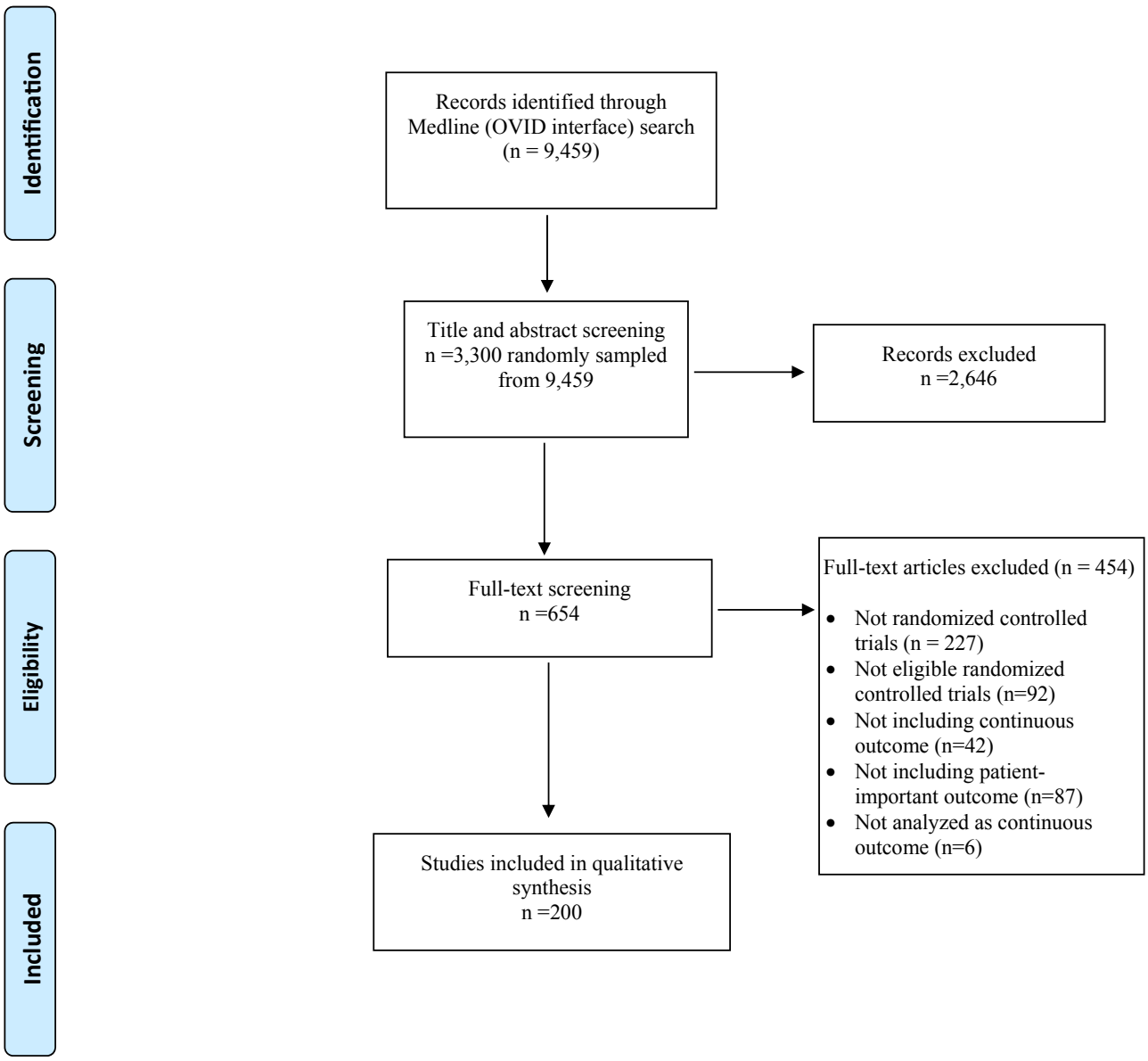

Fig. 1. PRISMA flow diagram.

0.29 (P = 0.001). Another significant beta coefficient indicated that there was a lower percentage of MPD when funding was not explicitly reported (beta coefficient 4.89 [0.40–9.38], P = 0.03). Type of intervention, journal, and allocation concealment proved not to be significant predictors for the percentage of MPD.

3.3. Categories of trial participants trial investigators considered as having MPD

Appendix D at www.jclinepi.com provides data regarding studies' reports of the reasons for MPD. Of 200 included studies, 24 explicitly reported absence of MPD, the remaining 176 studies potentially had MPD. The most frequently considered categories for potential MPD were "withdrew consent" (81 trials, 46.0%) and "experienced adverse event" (41 studies, 23.3%).

3.4. Analyses reported in the methods section regarding MPD

Table 4 presents the analysis plan reported in the methods section of included trials. Among all 200 included studies, 58 (29%) and 21 (10.5%) reported, in the methods section of their article, a plan to handle MPD in their primary and sensitivity analysis, respectively. The most frequent approaches specified were last observation carried forward (LOCF) (11, 5.5%) and mixed-effect model (11, 5.5%) for the primary analysis, and multiple imputation (MI) for the sensitivity analysis.

Table 1. General characteristics of 200 included trials to determine effect of missing participant data on outcomes

Variable	*n* (%)
Outcome classification	
Efficacy	191 (95.5)
Safety	9 (4.5)
Types of chosen outcome	
Length of stay (in hospital, intensive care unit)	25 (12.5)
Symptoms	84 (42.0)
Quality of life	44 (22.0)
Functional status	33 (16.5)
Disease severity	8 (4.0)
Length of drug use	6 (3.0)
Intervention	
Pharmacological	86 (43.0)
Surgical	24 (12.0)
Invasive nonsurgical procedure	14 (7.0)
Rehabilitation	24 (12.0)
Behavioral intervention	24 (12.0)
Diagnostic test	1 (0.5)
Complementary and alternative medicine	3 (1.5)
Other	24 (12.0)
Control	
Standard care	47 (23.5)
Placebo/sham	61 (30.5)
Pharmacological	31 (15.5)
Surgical	16 (8.0)
Invasive nonsurgical procedure	7 (3.5)
Rehabilitation	12 (6.0)
Behavioral intervention	10 (5.0)
Diagnostic test	1 (0.5)
Number of centers	
Single center	102 (51.0)
Multicenters	98 (49.0)
Journal types	
Top 5 journals	37 (18.5)
Nontop 5 journals	163 (81.5)
Arms	
2 arms	154 (77.0)
More than 2 arms	46 (33.0)
Funding[a]	
Private for profit (only provide drugs)	35 (17.5)
Private for profit (provide things other than drugs)	38 (19.0)
Private not for profit	72 (36.0)
Governmental	78 (39.0)
Not funded	13 (6.5)
Not reported	25 (12.5)

[a] Adds up to more than 200 because some trials have more than one source of funding.

Table 2. Methodological characteristics of 200 included trials to determine effect of missing participant data on outcomes

Variable	*n* (%)
Allocation concealment[a]	
Adequate	139 (69.5)
Inadequate	61 (30.5)
Blinding[b]	
Patients	99 (49.5)
Providers	80 (40.0)
Data collectors	106 (53.0)
Outcome adjudicators	105 (52.5)
Data analysts	21 (10.5)
No early stopping for benefit	**198 (99.0)**[c]
Primary analysis authors described	
Analysis described as intention to treat	5 (2.5)
Analysis described as modified intention to treat	94 (47.0)
Analyzed participants for whom outcome data were available in group to which they were randomized	11 (5.5)
No explicit statement	63 (31.5)
Per protocol analysis	27 (13.5)

[a] Allocation concealment refers to judgment of "definitely concealed" or "probably concealed."

[b] Blinding refers to judgment of "definitely blinded" or "probably blinded."

[c] 198 (99%) trials did not stop the investigation early for benefit.

3.5. Analyses conducted regarding MPD

Table 5 presents the analysis approaches authors used regarding MPD. Among 163 trials explicitly reporting the occurrence of MPD, it was unclear how trialists dealt with MPD in their primary analysis in 16 (9.8%) trials. Of the remaining 147 trials, 74 (45.4%) used complete case analysis, 35 (21.5%) all available data analysis, 9 (5.5%) LOCF, 10 (6.1%) mixed-effect model, 9 (5.5%) MI, 3 (1.8%) maximum likelihood, 2 (1.2%) mean imputation, 1 (0.6%) regression, and 4 (2.5%) methods other than the aforementioned. Very few (14, 8.6%) trials specified the missing mechanism when conducting an analysis regarding MPD; in 13 of 14 that did make such an explicit statement, the assumption was MAR (Table 4).

Of these 163 studies, 16 (9.8%) studies conducted sensitivity analysis for MPD (more than one sensitivity analysis can be conducted); multiple imputation (4, 2.5%), complete case analysis (3, 1.8%), LOCF (2, 1.2%), mean imputation (1, 0.6%), combination of more than one method (1, 0.6%), other methods not mentioned previously (2, 1.2%), and not reported (6, 4.5%). Five studies reported missing data assumptions used for the sensitivity analysis, and all of them used the same assumption as their primary analysis. The remaining 11 studies did not report whether they changed underlying missing data assumptions. Of the 16 trials that reported results of a sensitivity analyses to assess the impact of MPD, two reported that results were no longer statistically significant in one of their sensitivity analyses. Of 163 trials reporting the occurrence of MPD, 18 (11.1%) discussed the implications of MPD regarding risk of bias.

We could not perform the planned logistic regression to explore the factors associated with whether trials planned sensitivity analysis regarding MPD, due to the small number of studies conducting sensitivity analysis.

4. Discussion

4.1. Key findings

Of 200 RCTs, 187 (93.5%) made explicit statements regarding MPD, of which 24 (12%) reported no MPD and 163 (81.5%) reported that MPD had occurred, and its extent (Table 2). Very few investigators (16, 9.8%) compared baseline characteristics between patients with

Table 3. Reporting of information regarding missing participant data in included trials to determine effect of missing participant data on outcomes

Variable	*n* (%)
Among all included studies (*n* = 200)	
Explicit statement about missing participant data occurred in the main text or CONSORT flow diagram	
Yes, stated MPD occurred	163 (81.5)
Yes, stated MPD did not occur	24 (12.0)
No explicit statement	13 (6.5)
Among studies reported MPD occurred (*n* = 163)	
Assessment of baseline characteristics	
Yes, MPD group vs. non-MPD group	12 (7.4)
Yes, MPD in 1st arm vs. MPD in 2nd arm	2 (1.2)
Yes, they did both that mentioned previously	1 (0.61)
No	148 (90.8)
Reporting of MPD	
Separately reported for two arms	114 (69.9)
Reported overall only	5 (3.1)
Reported both per arm and overall	44 (27.0)

Abbreviation: MPD, missing participant data.

missing data and patients with complete data (Table 3). Many of these 163 trials reported substantial MPD (median 11.4%, Q1 2.5% to Q3 22.6%).

Among all 200 trials, less than a third (58 trials, 29%) reported in their methods a planned analytical approach to address MPD in their primary analysis and even fewer (21 trials, 10.5%) reported a plan for a sensitivity analysis (Table 4). Very few (14, 8.6%) trials specified the missing mechanism when conducting an analysis regarding MPD; in 13 of 14 that did make an explicit statement, the assumption was MAR (Table 5). The most common way trialists handled MPD was a complete case or all available data analysis (109, 67%). Other approaches included mixed-effect models (10, 6.1%), LOCF (9, 4.5%), and MI (9, 4.5%). Of the 163 trials with MPD, 16 (9.8%) conducted a sensitivity analysis.

Table 4. Method section reported analytic approach in 200 included trials for MPD on any continuous outcome

Variable	*n* (%)
Primary analysis	
Yes, reported in methods	58 (29.0)
No, did not report in the methods	142 (71)
What primary analysis was reported in methods (*N* = 58)	
Complete case analysis	9 (4.5)
All available data analyses	3 (1.5)
Mean imputation	3 (1.5)
Last observation carrying forward (LOCF)	11 (5.5)
Regression for MPD	1 (0.5)
Multiple imputation (MI)	9 (4.5)
Maximum likelihood (ML)	3 (1.5)
Mixed-effect model for missing data	11 (5.5)
Other	6 (3.0)
Not reported	2 (0.0)
Sensitivity analysis	
Yes, reported in methods	21 (10.5)
No, did not report in the methods	179 (89.5)
What sensitivity analysis was reported in methods (*N* = 21)	
Complete case analysis	3 (1.5)
Mean imputation	1 (0.5)
Last observation carrying forward (LOCF)	2 (1.0)
Regression for MPD	1 (0.5)
Multiple imputation (MI)	8 (4.0)
Mixed-effect model for missing data	1 (0.5)
Other	3 (1.5)
Not reported	2 (1.0)

Abbreviation: MPD, missing participant data.

Table 5. Reporting of information regarding analysis of missing participant data in included trials on patient-important outcomes

Variable	*n* (%)
Among studies reported MPD occurred (*N* = 163)	
Assumed missing mechanism when conduct analysis	
Missing at random	13 (7.9)
Ignorable missing	1 (0.7)
Not stated	149 (91.4)
Primary analysis	
Complete case analysis	74 (45.5)
All available data analyses	35 (21.5)
Mean imputation	2 (1.2)
Last observation carrying forward (LOCF)	9 (5.5)
Regression for MPD	1 (0.6)
Multiple imputation (MI)	9 (5.5)
Maximum likelihood (ML)	3 (1.8)
Mixed-effect model for missing data	10 (6.1)
Other	4 (2.5)
Unclear	16 (9.8)
Provide justification for the method used to handle MPD in the primary analysis	9 (5.5)
Whether they conducted sensitivity analysis regarding MPD for chosen outcome	
Yes	16 (9.8)
No	147 (90.2)
Implications of MPD regarding risk of bias discussed	18 (11.0)
Among studies conducted sensitivity analysis regarding MPD (*N* = 16)[a]	
Complete case analysis	3 (1.8)
Mean imputation	1 (0.6)
Last observation carrying forward (LOCF)	2 (1.2)
Multiple imputation (MI)	4 (2.5)
Combination of more than one method above for MPD	1 (0.6)
Other	2 (1.2)
Not reported	6 (4.5)
Sensitivity analysis changed the statistical significant result	2 (1.2)

Abbreviation: MPD, missing participant data.

[a] *N* = 16; it is possible that there are more than one sensitivity analysis.

4.2. Strengths and limitations of study

Strengths of our study include a systematic and comprehensive search, independent and duplicate screening and data abstraction, and a focus on patient-important continuous outcomes. We also implemented standardized built-in instructions in both screening and data abstraction forms on the Web-based systematic review software and

conducted calibration exercises. Our random sample of eligible studies from the 119 core medical journals published in 2014 ensures high representativeness of the recent practice among trialists [23–25].

With regard to limitations, we captured only the information authors reported in the publication and in the additional information provided in the appendix and supplementary data files. Authors may have conducted analyses regarding MPD beyond what they reported—contact with authors, which we did not undertake, could have provided additional information in this regard. We could also have checked registered protocols of trials for their MPD analyses plan when applicable. We did not collect data regarding whether the continuous outcomes selected are single or repeated measured outcomes. Collecting such information might provide more details on the different approaches of analyzing MPD on these two types of continuous outcomes. Finally, we could have adjusted for potential clustering effect for papers published in the same journal since they might have followed the same requirement from the journal to report the article in a certain manner.

4.3. Relation to other studies

Akl et al. [12] investigated the extent of MPD, the reporting, and the impact on results associated with MPD in studies addressing binary outcomes in five general prestigious medical journals. They found 13% of the trials did not report whether MPD occurred and 20% did not clearly report the analytical approaches used to handle MPD. These results are very similar to what we found with respect to continuous outcomes. Alshurafa et al. [26] investigated how methodological articles defined intention to treat (ITT) analysis in the context of MPD. They found the most frequently mentioned strategies suggested to deal with MPD within ITT were LOCF (50%), sensitivity analysis (50%), and imputation (46%). We found investigators took advantage (though infrequently) of a wider variety of sophisticated statistical strategies, and did not frequently use LOCF. Fiero et al. [27] conducted a systematic survey on how cluster RCTs dealing with MPD for their primary analysis. They found 19% of participants have missing data and the most common method to handle MPD is complete case analysis (44, 55%). Bell et al. [28] conducted a review of how RCTs handle missing data in the *BMJ*, *JAMA*, *Lancet*, and *New England Journal of Medicine* excluding cluster randomized trials and trials with primary outcome as survival data. Among 77 included trials, the median percentage of participants with missing outcome was 9% (range 0–70%) and 27 (35%) trials with missing data reported a sensitivity analysis. Existing review on methods regarding binary outcomes, cluster RCTs and top medical journals appears to be consistent with what we found for continuous outcomes in RCTs.

4.4. Interpretation of findings

In a recently conducted systematic survey [29] we conducted on the performance of methods of handling continuous MPD, LOCF proved to be much worse, particularly with respect to bias, than other methods investigated. In our study, investigators seem aware of the limitations of LOCF, with only 9 of 200 studies using the method, possibly much less than in the past. On the other hand, mixed-effects models or multiple imputation, approaches that proved to have excellent properties in the studies summarized in the survey, were used no more frequently than LOCF.

We found an association between explicit reporting of MPD with explicit reporting of funding. This suggests an association between not reporting MPD and poor reporting of other trial aspects. We also found trials with larger sample size had larger percentages of missing data. This finding highlights both the challenges of minimizing MPD in larger trials and enhances the importance of planning optimal analytical strategies to handle potential MPD.

4.5. Implications for trialists

Trial investigators should be more explicit in providing details on the reporting of MPD both at participant level and at outcome level, particularly when trials have multiple follow-up times as is commonly seen in the context of continuous outcomes. Reporting only the number of patients missing without specification of MPD at outcome level may omit key information.

Ideally, investigators will institute measures to minimize MPD [30]. MPD is often, however, inevitable, and implementation of optimal analytic strategies to deal with MPD would be highly desirable. These strategies include developing in advance a plan to deal with MPD and reporting that plan in their protocol and ultimately in the methods section of articles. Investigators should determine if baseline characteristics and other covariates differ between patients with missing data and patients with complete data. Differences in characteristics suggest that data might be MAR or that they could even be NMAR. Furthermore, they should examine the relation between patients' characteristics and observed outcomes; if there are substantial associations, it also suggests that, to some extent, the data are MAR and that imputation and data augmentation methods may be useful, at least as sensitivity analyses. Because it is very likely that in most cases both MAR and NMAR mechanisms are at play, sensitivity analysis testing assumptions about missing data should also be a standard of practice.

Investigators should be aware of the current optimal methods for handling MPD such as mixed-effect models and avoid using poorer performing methods such as LOCF or other single imputation methods [29]. The use of more sophisticated methods is likely to require help from

statisticians. Investigators should provide a justification for the sensitivity analyses they choose and discuss the implication of sensitivity analyses of MPD regarding risk of bias.

4.6. Implications for systematic reviewers

When judging the risk of bias of included trials, systematic reviewers should examine the quality and extent of reporting MPD in CONSORT and text of the trials at an outcome of interest level. Furthermore, they should examine the sensitivity analysis regarding MPD conducted in individual trials; this may provide a sense of the extent of risk of bias related to MPD across studies. These results may influence the application of across-trial methods to estimate the impact of MPD on risk of bias across the body of evidence [31,32].

4.7. Implications for future research

A checklist addressing the reporting of analysis regarding MPD in RCTs may be useful for both evaluating and optimizing analytic strategies in studies of continuous outcomes. Further investigation might focus on optimal approaches to conducting sensitivity analysis regarding MPD.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jclinepi.2017.05.017.

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