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REVIEW

# Potentially missing data are considerably more frequent than definitely missing data: a methodological survey of 638 randomized controlled trials

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## Abstract

**Background and Objective:** Missing data for the outcomes of participants in randomized controlled trials (RCTs) are a key element of risk of bias assessment. However, it is not always clear from RCT reports whether some categories of participants were followed-up or not (i.e., do or do not have missing data) nor how the RCT authors dealt with missing data in their analyses. Our objectives were to describe how RCT authors (1) report on different categories of participants that might have missing data, (2) handle these categories in the analysis, and (3) judge the risk of bias associated with missing data.

**Methods:** We surveyed all RCT reports included in 100 clinical intervention systematic reviews (SRs), half of which were Cochrane SRs. Eligible SRs reported a group-level meta-analysis of a patient-important dichotomous efficacy outcome, with a statistically significant effect estimate. Eleven reviewers, working in pairs, independently extracted data from the primary RCT reports included in the SRs. We predefined 19 categories of participants that might have missing data. Then, we classified these participants as follows: ‘‘explicitly followed-up,’’ ‘‘explicitly not followed-up’’ (i.e., definitely missing data), or ‘‘unclear follow-up status’’ (i.e., potentially missing data).



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**Results:** Of 638 eligible RCTs, 400 (63%) reported on at least one of the predefined categories of participants that might have missing data. The median percentage of participants who were explicitly not followed-up was 5.8% (interquartile range 2.2−14.8%); it was 9.7% (4.1−14.9%) for participants with unclear follow up status; and 11.7% (interquartile range 5.6−23.7%) for participants who were explicitly not followed-up and with unclear follow-up status. When authors explicitly reported not following-up participants, they most often conducted complete case analysis (54%). Most RCTs neither reported on missing data separately for different outcomes (99%) nor reported using a method for judging risk of bias associated with missing data (95%).

**Conclusion:** ''Potentially missing data'' are considerably more frequent than ''definitely missing data.'' Adequate reporting of missing data will require development of explicit standards on which editors insist and to which RCT authors adhere. 

*Keywords:* Missing data; Follow-up; Reporting; Risk of bias; Randomized controlled trials; Systematic reviews; Meta-analysis

## 1. Background

Missing data for the outcomes of participants may threaten the validity of results of randomized controlled trials (RCTs) and systematic reviews (SRs) that include those RCTs [1]. Although missing data reduce power because of participant losses and likely increases the risk of bias particularly when missingness is associated with the occurrence of the outcome, limitations in its reporting and analysis further undermine validity. A survey of more than 200 RCTs showed that substantial discrepancy exists between proposed methodologies and current practice in handling, analysis, and reporting of missing data for patient-reported outcome measures in RCTs [2].

RCT authors typically report missing data by participant and not by outcome [3]. Consequently, when RCT authors report that a participant is lost to follow-up, SR authors might conclude that data are missing for all outcomes of interest. Nevertheless, it is possible that this participant might have experienced an event for a certain outcome before the date of premature end of follow-up. When this RCT contributed to a meta-analysis, this scenario could introduce bias whether the SR authors conduct a complete case analysis or make assumptions regarding the different outcomes of the participants with missing data.

Also, RCT authors may not report clearly whether they followed up participants in certain categories, for example, whether nonadherent participants did or did not have missing data [3]. Although RCT authors should follow-up nonadherent participants and use their outcome information in the analysis [4], many wrongly equate nonadherence with missing data [5].

Marciniak et al. compared the loss to follow-up rates in published reports of RCTs of oral antithrombotic, agents with loss to follow-up rates calculated based on more detailed documents made available to the Food and Drug Administration (FDA) for the same RCTs [6]. They found a large discrepancy between the median of published rate of all ''missing follow-up categories'' (0.9%), and the median of the FDA-calculated loss to follow-up rates (13%). This suggests that missing data might be more frequent than what is explicitly reported and published.

It is also frequently unclear how RCT authors handle missing data in their analyses. A survey of RCTs published in three major pain journals between 2006 and 2012 found that only 45% of RCTs reported a statistical method to handle missing data in the primary meta-analysis [7]. Another review of RCTs reporting eight widely used patient-reported outcome measures found that almost half of the RCTs did not report a method to deal with missing data, three-quarters did not perform sensitivity analyses, and even fewer (16%) discussed the potential impact of missing data on their results [2].

The objective of this study was to assess the reported extent and handling of missing dichotomous outcome data in RCTs. Specifically, we examined whether and how RCT authors report on (1) the number of participants belonging to different categories that might have missing data, (2) the explicit reporting on the follow-up status of these participants, and (3) the handling of these participants in the main and secondary analyses.

## 2. Methods

### 2.1. Design overview

The current study is part of a larger project examining methodological issues related to missing data in SRs and RCTs [8]. We included reports of all RCTs that contributed to the main meta-analysis of the comparison and outcome addressed in a random sample of 100 eligible SRs. An eligible SR was either a Cochrane or a non-Cochrane SR published in 2012 reporting a group-level meta-analysis of a patient-important dichotomous efficacy outcome, with a statistically significant effect estimate.

Based on previous work, we developed a list of predefined categories of participants that might have missing data [1,8,9]. We refined the original list to accommodate new categories that emerged from data abstraction and did not fit existing categories. The labeling of these categories reproduces the wording used by the trial authors. Figure 1 lists the 19 final categories of participants that might have missing data (first column) and the reported follow-up status of participants (second column). To avoid confusion among categories with common words, we defined the following categories as follows:

- ''Ineligible participants or mistakenly randomized'': participants who were discovered to be ineligible after randomization, but the reason for ineligibility relates to a baseline characteristic;

**What is new?**

**Key findings**

- Potentially missing data is considerably more frequent than definitely missing data.

**What this adds to what was known?**

- None of the randomized controlled trials that imputed outcome, took into account the uncertainty associated with imputing outcomes.
- When studies explicitly reported not following-up participants, about half explicitly reported conducting a complete case analysis; almost all the remainder studies did not specify how they handled missing data in their analysis.

**What is the implication and what should change now?**

- Both randomized controlled trial authors and journals editors need to better address missing data in trials reports.
- Until reporting of missing data is more explicit and transparent, users of the medical literature should take into account potentially missing data in addition to definitely missing data.

- "Ineligible because of occurrence of outcome": participants who were eligible at baseline then developed the outcome at early stages of the trial. These are typically considered ineligible if the trialists judge that the occurrence of the outcome cannot be related to the intervention of interest;
- "Discontinued because of adverse events": participants who had adverse event and "discontinued" either the medication or the "trial";
- "Experienced adverse events": participants who developed side effects but without any indication of ""discontinuation."

We did not consider participants described as "dead" and "excluded as part of center exclusion" as categories that might have missing data.

Our published protocol includes further details regarding definitions, eligibility criteria, search strategy, and selection process of SRs [8]. Because it did not involve human participants, no ethical approval was required for the conduct of this study.

### 2.2. Data abstraction

We developed and pilot tested a standardized data abstraction form that included detailed instructions. We conducted calibration exercises to verify the accuracy and consistency of the data abstraction process. Eleven reviewers, working

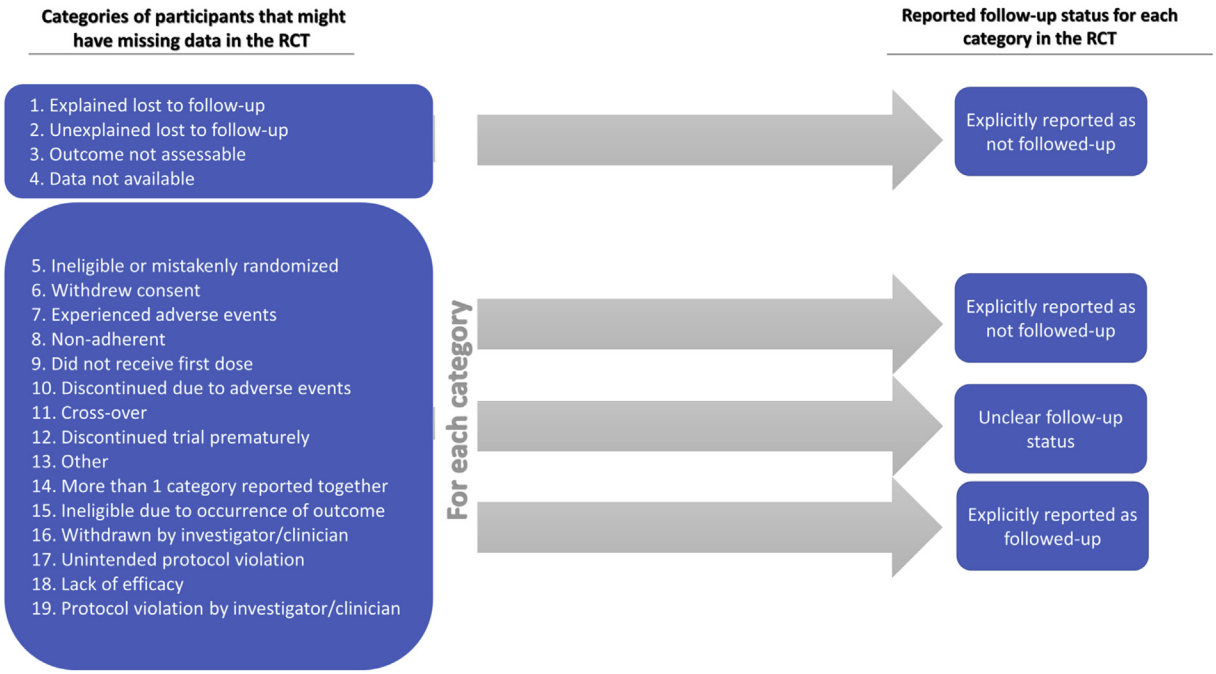


**Fig. 1.** The 19 final categories of participants that might have missing data and the reported follow-up status. RCT, randomized controlled trial. 5: "ineligible participants or mistakenly randomized": participants who were discovered to be ineligible after randomization, but the reason for ineligibility relates to a baseline characteristic; 7: "experienced adverse events": participants who developed side effects but without any indication of ""discontinuation"; 10: "discontinued because of adverse events": participants who had adverse event and "discontinued" either the medication or the "trial"; 15: "ineligible because of occurrence of outcome": participants who were eligible at baseline then developed the outcome at early stages of the trial. These are typically considered ineligible if the trialists judge that the occurrence of the outcome cannot be related to the intervention of interest.

in pairs and independently, abstracted data using the REDCap electronic data capture tool hosted at the American University of Beirut [10]. A core team (E.A.A., L.A.K., B.D., and A.D.) met regularly to discuss the progress and challenges encountered during data abstraction and suggested solutions that they communicated to the entire team. They conducted triplicate and independent data abstraction as needed to ensure the quality of the data.

As presented in the following, we collected the following data from all included RCT reports: (1) characteristics of the RCTs; (2) reporting in the results section on and handling of the predefined categories of missing data; (3) reporting on and handling of missing data as defined by RCT authors; and (4) assessment of risk of bias associated with missing data.

A. The characteristics of the RCTs:

1. Type of article (i.e., abstract, full-text article);
2. Language of report;
3. Type of source of funding;
4. Planned follow-up time for outcome of interest;
5. Time-to-occurrence for outcome of interest;
6. Number of participants randomized to each study arm;
7. Type of analysis (e.g., intention-to-treat [ITT], per protocol).

B. The reporting on and handling of the predefined categories of participants that might have missing data:

1. Reporting on participants belonging to each category in the results section, if applicable;
2. Number of participants belonging to each category;
3. Explicit reporting on follow-up status of participants within each category. We classified these participants as follows: ''explicitly followed-up'', ''explicitly not followed-up'' (i.e., definitely missing data), or ''unclear follow-up status'' (i.e., potentially have missing data);
4. Inclusion of participants of each category in the denominator of the analysis of interest;
5. Explicit statement of the analytical method for dealing with each category in the analysis of interest (i.e., when generating the best effect estimate).

C. The reporting on and handling of missing data as defined by RCT authors:

1. Explicit reporting on missing data in the results section for the specific outcome of the analysis of interest as opposed to reporting premature end of follow-up for RCT participants in general [3];
2. Reporting of the level of missing data (e.g., per arm, both arms combined);
3. Comparison of the baseline characteristics of participants with and without missing data (e.g., missing data group vs. nonmissing data group; missing data in intervention arm vs. missing data in control arm);
4. Comparison of the number of participants with missing data between the two study arms;
5. Description of the mechanism of missingness (e.g., missing at random);
6. Explicit statement taking into account uncertainty associated with imputing outcomes when calculating the confidence interval, in case imputation methods were used in the analysis of interest;
7. Justification for the analytical method used to handle missing data in the analysis of interest.

**Table 1.** General characteristics of the included randomized controlled trials ($n$ = 638)

| Variable | *N* (%) |
|---|---|
| Type of article | |
| Full-text article | 617 (96.7) |
| Abstract/research letter | 21 (3.3) |
| Year of publication (median [IQR]) | 2005 (1998–2008) |
| Language of report | |
| English | 606 (95) |
| Non-English | 32 (5) |
| Source of funding of trial | |
| Private for profit | 220 (34.5) |
| Private not for profit | 118 (18.5) |
| Government | 107 (16.8) |
| Not funded | 16 (2.5) |
| Not reported | 284 (44.5) |
| Type of intervention | |
| Pharmacologic | 382 (58.5) |
| Surgery/invasive procedure | 169 (25.9) |
| Other | 102 (15.6) |
| Planned follow-up time reported | 509 (79.8) |
| Planned follow-up time in months (median [IQR])[a] | 6 (1–12) |
| Time-to-occurrence reported | 95 (14.9) |
| Time-to-occurrence in months (median [IQR])[b] | 1 (0.5–6) |
| Number randomized, intervention group [median (IQR)] | 69 (31–167) |
| Number randomized, control group (median [IQR]) | 66 (32–162) |
| Reported type(s) of analyses | |
| ITT | 233 (36.5) |
| Modified ITT[c] | 21 (3.3) |
| Per protocol | 43 (6.7) |
| As treated | 12 (1.9) |
| None of the above | 388 (60.8) |

*Abbreviations*: ITT, intention-to-treat; IQR, interquartile range.
[a] $N$ = 509, number of trials reporting planned follow-up time.
[b] $N$ = 95, number of trials reporting time to occurrence.
[c] We reported on whether the authors reported on using ''modified ITT,'' either using the terminology explicitly or by describing a modification to the ITT analysis (i.e., analyzed all participants as they were randomized with the exception of certain category of participants they decided to exclude).

**Table 2.** Percentage of RCTs reporting on our predefined categories of participants that might have missing data ($n$ = 638 trials)

| | RCTs reporting on the category | RCTs reporting on follow-up status for each category[a] | | |
|---|---|---|---|---|
| **Categories** | ***N* (%)** | **Explicitly FU** | **Explicitly not FU** | **Unclear FU status** |
| Unexplained lost to follow-up | 161 (25.2) | 0 | 161 (100.0) | 0 |
| Ineligible or mistakenly randomized | 142 (22.3) | 10 (7.0) | 36 (25.4) | 96 (67.6) |
| Experienced adverse events | 135 (21.2) | 92 (68.1) | 0 | 43 (31.9) |
| Withdrew consent | 131 (20.5) | 6 (4.6) | 23 (17.6) | 102 (77.9) |
| Nonadherent | 131 (20.5) | 14 (10.7) | 15 (11.4) | 102 (77.9) |
| Did not receive the first dose | 89 (13.9) | 4 (4.5) | 12 (13.5) | 73 (82.0) |
| Discontinued because of adverse events | 75 (11.8) | 7 (9.3) | 23 (30.7) | 45 (60.0) |
| Cross-over | 62 (9.7) | 21 (33.9) | 2 (3.2) | 39 (62.9) |
| Discontinued trial prematurely | 55 (8.6) | 8 (14.5) | 4 (7.3) | 43 (78.2) |
| Other[b] | 41 (6.4) | 1 (2.4) | 5 (12.2) | 35 (85.4) |
| Explained lost to follow-up | 30 (4.7) | 0 | 30 (100.0) | 0 |
| More than one category reported together | 28 (4.4) | 1 (3.6) | 6 (21.4) | 21 (75.0) |
| Outcome not assessable | 18 ‘(2.8) | 0 | 18 (100) | 0 |
| Data not available | 18 (2.8) | 0 | 18 (100.0) | 0 |
| Ineligible because of occurrence of outcome | 14 (2.2) | 1 (7.1) | 1 (7.1) | 12 (85.8) |
| Withdrawn by investigator/clinician | 13 (2.0) | 0 | 4 (30.8) | 9 (69.2) |
| Unintended protocol violation | 9 (1.4) | 1 (11.1) | 1 (11.1) | 7 (77.8) |
| Lack of efficacy | 8 (1.3) | 0 | 2 (25.0) | 6 (75.0) |
| Protocol violation by investigator/clinician | 4 (0.6) | 0 | 1 (25.0) | 3 (75.0) |

*Abbreviations*: FU, followed-up; RCT, randomized controlled trial.
[a] The denominator is the number of trials reporting on this category.
[b] Two trials listed a second category as ‘‘other,’’ the percentages of participants were 0.4% and 2.4%. Both trials did not explicitly report on the follow-up status of these participants.

D. The assessment of the risk of bias associated with missing data:

   1. Method(s) used to judge risk of bias associated with missing data (sensitivity analysis, e.g., complete case analysis, assumptions).

We also asked the data abstractors about their perception of the clarity of reporting of missing data in the included RCTs. We did not follow strict criteria to complete this answer, but the judgment was driven by the amount of time and effort spent to abstract information on all the previous variables.

### 2.3. Data analysis

We conducted a descriptive analysis of all variables. For categorical variables, we reported frequencies and percentages. For continuous variables, which were not normally distributed, we used median and interquartile range (IQR). We calculated the percentage of RCTs that reported on each category of participants that might have missing data. In addition, for each category, we calculated the percentage of RCTs that (1) explicitly reported following-up participants, (2) explicitly reported not following-up participants, and (3) did not provide explicit reporting on the follow-up status. We created a variable called ‘‘all categories combined’’ which includes for each RCT, the participants that belonged to at least 1 of the 19 categories.

We also explored the association between trial sponsorship and reporting on at least one of the predefined categories of participants that might have missing data.

Then, we calculated the percentage of participants belonging to each of the 19 categories of participants separately and for all categories combined. We then calculated the distribution (median and IQR) of these percentages across RCTs.

To assess the potential impact of missing data on study effect estimates, we calculated for each RCT that reported on at least one category of participants that might have missing data, the ratio of the percentage of participants with missing data to the difference in the event rates (denominator being number randomized) between the two arms (please see Supplementary File). We clarify the calculation in an example in Supplementary File. We then calculated the median and IQR for the distribution of these ratios across RCTs. We made these calculations twice: first, considering participants who were explicitly not followed-up; second, considering both participants who were explicitly not followed-up and those with unclear follow-up status. For all analyses, we used SPSS statistical software, V.21.0 (SPSS INC, Chicago, IL, USA).

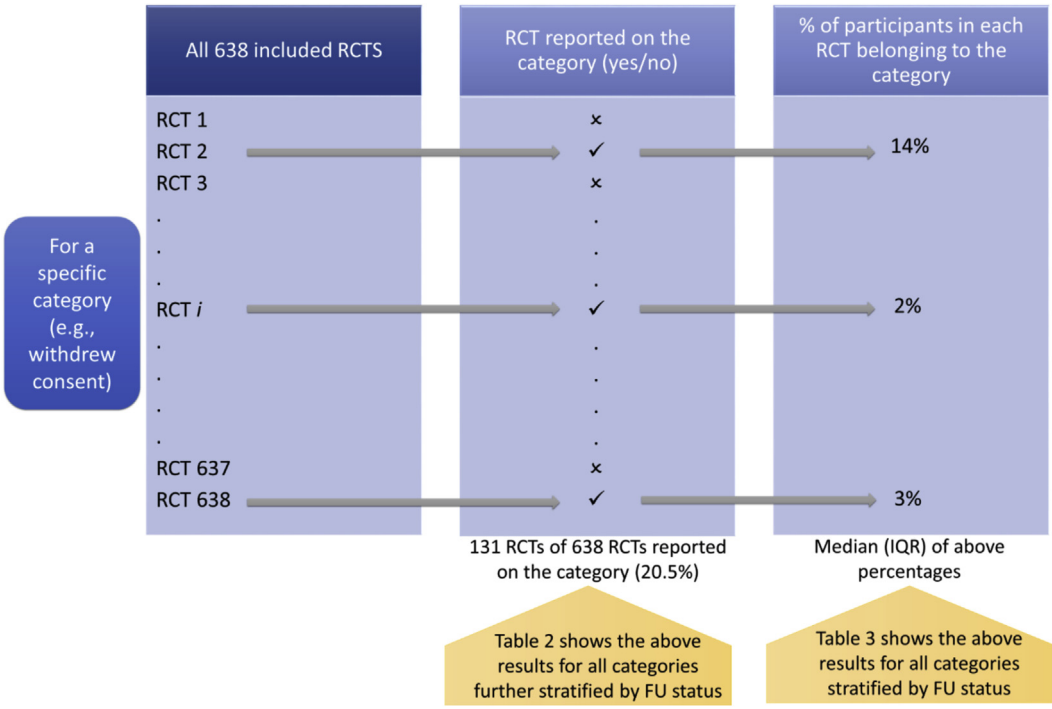


**Fig. 2.** Explanation of information reported in Tables 2 and 3 based on an example of reporting on the category ''withdrew consent'' by the 638 RCTs. FU, follow-up; IQR, interquartile range; RCT, randomized controlled trial.

**Table 3.** Distribution of percentages of participants across the randomized clinical trials belonging to each category according to follow-up status

| | Explicitly not FU | | Unclear FU status | | Explicitly not FU and unclear FU status | |
|---|---|---|---|---|---|---|
| **Categories** | **No. of RCTs** | **Median % (IQR)** | **No. of RCTs** | **Median % (IQR)** | **No. of RCTs** | **Median % (IQR)** |
| Unexplained lost to follow-up | 161 | 4.1 (1.2–10.3) | 0 | – | 161 | 4.1 (1.2–10.3) |
| Ineligible or mistakenly randomized | 36 | 4.1 (1.8–10.0) | 96 | 2.3 (1.0–6.5) | 132 | 2.9 (1.0–7.7) |
| Experienced adverse events | 0 | – | 43 | 11.0 (4.4–37.2) | 43 | 11.0 (4.4–37.2) |
| Withdrew consent | 23 | 3.7 (1.7–5.7) | 102 | 2.6 (1.1–6.3) | 125 | 2.9 (1.1–6.1) |
| Nonadherent | 15 | 3.3 (1.7–8.2) | 102 | 6.9 (1.8–15.1) | 117 | 5.4 (1.8–14.5) |
| Did not receive the first dose | 12 | 1.0 (0.5–1.7) | 73 | 1.6 (0.9–3.6) | 85 | 1.3 (0.9–3.1) |
| Discontinued because of adverse events | 23 | 3.7 (2.2–6.5) | 45 | 4.0 (2.1–6.1) | 68 | 4.0 (2.2–6.3) |
| Cross-over | 2 | 4.3, 11.0 | 39 | 3.0 (1.2–5.0) | 41 | 3.3 (1.3–5.3) |
| Discontinued trial prematurely | 4 | 4.9 (0.9–10.7) | 43 | 6.3 (3.5–18.1) | 47 | 6.3 (3.2–16.4) |
| Other | 5 | 1.5 (0.9–2.4) | 35 | 2.1 (1.0–4.1) | 40 | 2.1 (1.0–4.0) |
| Explained lost to follow-up | 30 | 3.6 (2.0–7.3) | 0 | – | 30 | 3.6 (2.0–7.3) |
| More than one category reported together | 6 | 10.7 (3.9–18.7) | 21 | 5.4 (3.5–9.2) | 27 | 6.5 (4.1–13.4) |
| Outcome not assessable | 18 | 27.3 (3.7–28.7) | 0 | – | 18 | 27.3 (3.7–28.7) |
| Data not available | 18 | 2.6 (0.9–5.3) | 0 | – | 18 | 2.6 (0.9–5.3) |
| Ineligible because of occurrence of outcome | 1 | 4.3 | 12 | 1.9 (0.3–4.1) | 13 | 2.4 (0.4–4.2) |
| Withdrawn by investigator/clinician | 4 | 1.5 (0.9–3.0) | 9 | 0.9 (0.4–5.8) | 13 | 1.3 (0.6–4.2) |
| Unintended protocol violation | 1 | 0.4 | 7 | 1.4 (0.3–4.9) | 8 | 0.9 (0.3–4.9) |
| Lack of efficacy | 2 | 0.1, 7.9 | 6 | 2.5 (1.2–6.2) | 8 | 2.5 (0.6–7.9) |
| Protocol violation by investigator/clinician | 1 | 0.3 | 3 | 0.6, 0.7, 1.3 | 4 | 0.7 (0.4–1.2) |
| All categories combined | 256 | 5.8 (2.2–14.8) | 288 | 9.7 (4.1–19.9) | 400 | 11.7 (5.6–23.7) |

*Abbreviations:* FU, followed-up; IQR, Interquartile range; RCT, randomized controlled trial.

## 3. Results

Of 653 RCTs included in the 100 eligible SRs, we could not retrieve the full texts for 15 (2.3%), despite extensive efforts by librarians. Table 1 reports the general characteristics of the 638 included RCTs. The median date of publication was 2005. Most were published in English (94%), reported source of funding (55%), reported planned follow-up time (80%), assessed a pharmacologic intervention (56%), but did not report type of analysis (e.g., ITT, per protocol; 61%). The median planned follow-up time of the outcome of interest was 6 months, and the median time-to-occurrence was 1 month. The median numbers of participants randomized to the intervention and control arms were 69 (31–167) and 66 (32–162), respectively.

### 3.1. Reporting on and handling of the predefined categories of missing data

Table 2 shows the reporting, in the results section, on each of the predefined categories of missing data (please refer to Fig. 2 for explanation of what Table 2 reports).

The top reported categories were "unexplained lost to follow-up" (25%) and "ineligible or mistakenly randomized" (22%). The least reported categories were "protocol violation by investigator or clinician" (0.6%) and "lack of efficacy" (1.3%). Considering the categories separately, only for the one category "experienced adverse events," a majority of the RCTs (68%) explicitly reported following-up participants. For the remaining categories excluding those who were explicitly followed-up, most RCTs did not explicitly report on whether they followed-up participants (range 60–86%).

The distribution of all 638 RCTs according to their reporting on categories of participants that might have missing data was as follows:

- One hundred eighty-seven RCTs (29%) did not report on any category of participants that might have missing data;
- Fifty-one RCTs (8%) reported on at least one category of participants who were explicitly followed-up;
- Four hundred RCTs (63%) reported on at least one category of participants that were either explicitly not followed-up or with unclear follow-up status.

**Table 4.** Handling in the primary analysis of the predefined categories of participants who were explicitly not followed-up or with unclear follow-up status

| | Dealing method in the analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Explicitly not followed-up | | | | Unclear follow-up status | | | |
| Categories | *n* | CCA | Other method[a] | NR | *n* | CCA | Other method[a] | NR |
| Unexplained loss to follow-up | 161 | 74 (46.0) | 5 (3.1) | 82 (50.9) | 0 | 0 | 0 | 0 |
| Ineligible or mistakenly randomized | 36 | 33 (91.7) | 0 | 3 (8.3) | 96 | 47 (49.0) | 0 | 49 (51.0) |
| Experienced adverse events | 0 | 0 | 0 | 0 | 43 | 0 | 0 | 43 (100.0) |
| Withdrew consent | 23 | 13 (56.5) | 1 (4.3) | 9 (39.2) | 102 | 31 (30.4) | 2 (2.0) | 69 (67.6) |
| Nonadherent | 15 | 11 (73.3) | 1 (6.7) | 3 (20.0) | 102 | 25 (24.5) | 1 (1.0) | 76 (74.5) |
| Did not receive the first dose | 12 | 11 (91.7) | 0 | 1 (8.3) | 73 | 37 (51.7) | 0 | 36 (49.3) |
| Discontinued because of adverse events | 23 | 8 (34.8) | 1 (4.3) | 14 (60.9) | 45 | 12 (26.7) | 0 | 33 (73.3) |
| Cross-over | 2 | 1 (50.0) | 0 | 1 (50.0) | 39 | 2 (5.1) | 1 (2.6) | 36 (92.3) |
| Discontinued trial prematurely | 4 | 3 (75.0) | 0 | 1 (25.0) | 43 | 7 (16.3) | 1 (2.3) | 35 (81.4) |
| Other | 5 | 2 (40.0) | 1 (20.0) | 2 (40.0) | 35 | 5 (14.3) | 0 | 30 (85.7) |
| Explained loss to follow-up | 30 | 9 (30.0) | 0 | 21 (70.0) | 0 | 0 | 0 | 0 |
| More than one category reported | 6 | 2 (33.3) | 0 | 4 (66.7) | 21 | 10 (46.7) | 2 (9.5) | 9 (42.8) |
| Outcome not assessable | 18 | 11 (61.1) | 0 | 7 (38.9) | 0 | 0 | 0 | 0 |
| Data not available | 18 | 13 (72.2) | 2 (11.1) | 3 (16.7) | 0 | 0 | 0 | 0 |
| Ineligible because of occurrence of outcome | 1 | 0 | 0 | 1 (100.0) | 12 | 5 (41.7) | 0 | 7 (58.3) |
| Withdrawn by investigator/clinician | 4 | 2 (50.0) | 0 | 2 (50.0) | 9 | 1 (11.1) | 0 | 8 (88.9) |
| Unintended protocol violation | 1 | 1 (100.0) | 0 | 0 | 7 | 3 (42.9) | 0 | 4 (57.1) |
| Lack of efficacy | 2 | 0 | 0 | 2 (100.0) | 6 | 1 (16.7) | 0 | 5 (83.3) |
| Protocol violation by investigator/clinician | 1 | 1 (100.0) | 0 | 0 | 3 | 1 (33.3) | 0 | 2 (67.7) |
| Total | 362 | 195 (53.9) | 11 (3.0) | 156 (43.1) | 636 | 187 (29.4) | 7 (1.1) | 442 (69.5) |

*Abbreviations*: CCA, complete case analysis; NR, not reported; RCTs, randomized controlled trials.

Each RCT could have mentioned more than one category, resulting in a total of 998 instances ($n = 400$ RCTs that reported at least one category of missing data in the results section).

[a] Other method: including making assumptions and imputations.

**Table 5.** Reporting on, handling of, and assessing risk of bias associated with missing data as defined by trial authors ($n$ = 400 randomized controlled trials that reported at least one category of missing data in the results section)

| Variable | *N* (%) |
|---|---|
| Missing data explicitly reported in the results section | |
| Not separate for different outcomes | 397 (99.3) |
| For each outcome separately | 3 (0.7) |
| Number of participants with missing data reported | |
| Yes, overall (both arms combined) | 105 (26.2) |
| Yes, per arm | 352 (88.3) |
| No | 7 (1.8) |
| Baseline characteristics of participants with missing data reported | |
| Yes, missing data group vs. nonmissing data group | 7 (1.7) |
| Yes, missing data in intervention arm vs. missing data in control arm | 4 (1.0) |
| No | 389 (97.3) |
| Number of participants with missing data compared between the two study arms | 24 (6.0) |
| Mechanisms of missingness for missing data described the missing data (e.g., missing completely at random, missing not at random) | 3 (0.7) |
| Uncertainty associated with imputing outcomes taken into account, in case imputation was done | |
| Imputed outcomes and took uncertainty into account | 0 |
| Imputed outcomes but did not take uncertainty account | 13 (3.2) |
| Not applicable, no imputation for missing data | 387 (96.8) |
| Justification for the method used to handle missing data provided | |
| Yes | 2 (0.5) |
| No, missing data were handled but not justified | 190 (47.5) |
| Not applicable, missing data were not handled | 208 (52.0) |
| Method reported to be used for judging risk of bias associated with missing data | |
| Complete case analysis | 6 (1.5) |
| None had event | 5 (1.2) |
| All had event | 3 (0.7) |
| Same event rate | 0 |
| Worst-case scenario | 5 (1.2) |
| Best-case scenario | 3 (0.7) |
| Other[a] | 3 (0.7) |
| Single imputation | 0 |
| Multiple imputations | 0 |
| Mixed effect model | 0 |
| Unclear which method used | 4 (1.0) |
| No method reported | 378 (94.5) |

[a]Other methods included.

- Compared the effectiveness of intervention between completed and censored participants.
- Assumed rate of primary efficacy endpoint in sensitivity analysis adjusted for missing values during intended treatment period—primary subjects and nonprimary subjects.
- Treated participants who withdrew were lost to follow-up or died as censored data for survival analysis if the event under investigation had not occurred.

Table 3 shows the distribution of percentages of participants across the RCTs belonging to each category according to follow-up status (please refer to Fig. 2 for explanation of what Table 3 reports). The categories with the largest median percentages of participants were "outcome not assessable" (27.3%, IQR 3.7–28.7%) and "experienced adverse events" (18.3%, IQR 7.2–46.2%). The three categories with the smallest median percentages of participants were "withdrawn by investigator or clinician" (1.3%, IQR 0.6–4.2%), "did not receive the first dose" (1.4%, IQR 0.9–3.1%), and "unintended protocol violation" (1.4%, IQR 0.3–4.9%).

Among 256 RCTs that explicitly reported on participants who were explicitly not followed-up for at least one of the predefined categories, the median percentage for all categories combined was 5.8% (IQR 2.2–14.8%). Among 288 RCTs that mentioned at least one of the predefined categories of participants with unclear follow-up status, the median percentage for all categories combined was 9.7% (IQR 4.1–19.9%). Among 400 RCTs that reported on participants that were either explicitly not followed-up or with unclear follow-up status for at least one of the predefined categories, the median percentage for all categories combined was 11.7% (IQR 5.6–23.7%).

Table 4 shows the handling in the primary analysis of each of the predefined categories of participants that were either explicitly not followed-up or with unclear follow-up status by the 400 RCTs that reported on at least one of those categories. We present these handling methods according to the follow-up status of these participants. Each of the 400 RCT could have reported on more than one category, resulting in a total of 998 instances where categories were mentioned:

- In the 362 instances in which the authors explicitly reported not following-up participants, 54% reported using complete case analysis, 43% did not report how they dealt with missing data, and 3% reported using another specific method (e.g., none had the event, all had the event, multiple imputations, best-case scenario);
- In the 636 instances in which the authors did not explicitly report on the follow-up status of

participants, 70% did not report how they dealt with participants with potential missing data, 29% reported using complete case analysis, and 1% reported using another specific method.

### 3.2. Reporting on and handling of missing data as defined by RCT authors

Table 5 shows the reporting on, handling of, and assessing risk of bias associated with missing data as defined by the RCT author. These participants who might have missing data include both participants who were explicitly not followed-up and participants with unclear follow-up status. Among the 400 RCTs that reported at least one category of participants that might have missing data in the results section, the majority reported the number of participants with missing data per arm (88%). However, a minority of those RCTs reported on missing data separately for different outcomes (1%), compared the baseline characteristics of participants with and without missing data separately for each study arm (2%) or of participants with missing data separately between the two study arms (1%) or compared the number of participants with missing data separately between the two study arms (6%). Only three studies (0.7%) described mechanisms of missingness (e.g., missing completely at random, missing not at random) of participants with missing data. None of the 13 RCTs that imputed outcomes took uncertainty into account when calculating the confidence interval. Only, three RCTs presented a justification for their approach to handle missing data (0.5%). In addition, 95% did not report using a method for judging risk of bias associated with missing data.

### 3.3. Clarity of reporting of missing data

Reviewers' judgment on whether the reporting of missing data was clear was as follows: 34% agreed, 36% were neutral, and 30% disagreed. The agreement between the pairs of reviewers on those judgments was good (Kappa = 0.731). Box 1 lists examples of the challenges that the reviewers faced during data abstraction and management and how they addressed them.

### 3.4. Ratio of rate of missing data to the risk difference

The ratio of the rate of missing data relative to the risk difference for participants who were explicitly not followed-up was median 0.6, IQR 0.0–3.0. When included in this analysis both participants who were explicitly not followed-up and those with unclear follow-up status, the ratio rises to a median of 1.7, IQR 0.5–9.1.

## 4. Discussion

### 4.1. Summary of findings

Of 638 included RCTs, about two-thirds mentioned in their results section at least one of the predefined categories

**Box 1.** Examples of challenges met during data abstraction and management and the solutions adopted to address them

| Challenge | Solution |
|---|---|
| • Certain categories of participants that might have missing data reported by RCT authors did not fit in the original list of those categories. | • We refined the original list to accommodate new categories that emerged from data abstraction and did not fit already defined categories. |
| • Trial author may have counted some participants under more than one of the predefined categories of participants that might have missing data, e.g., "discontinued trial prematurely" and "nonadherent."<br>• In some instances, this double counting was obvious (e.g., in the CONSORT flow diagram); in others, it was not. | • Whenever double counting was obvious, we listed these participants under only one category. |
| • Some RCTs did not clearly report the number of events of the completers. | • We used the number of events as reported in the meta-analysis; we implicitly assumed that the SR authors used accurate numbers (e.g., by contacting the RCT authors). |
| • Few RCTs excluded participants with available outcome data. | • We considered these participants as not having missing data. |
| • Some RCTs reported on the percentages of participants belonging to the predefined categories but not their count. It was not clear whether the denominator was the number of participants randomized, the number of participants who received treatment, or number of participants who were compliant. | • We made our best guess of which denominator the authors used. When that was not possible, we used the number of participants randomized. |
| • In some instances, the population of interest of the SR was a subgroup population of the included RCT, and the RCT authors did not report on the categories of missing data within that subgroup. | • For each category, we multiplied the number of participants with missing data in the overall study population by the proportion of the participants in the subgroup of interest |

*Abbreviations:* RCTs, randomized controlled trials; SR, systematic reviews.

of participants that might have missing data. The median percentage of participants who were explicitly not followed-up was 5.8% (IQR 2.2−14.8%). When one also includes participants with unclear follow-up status, the total value rises to 11.7% (IQR 5.6−23.7%).

When authors explicitly reported not following-up participants, 54% explicitly reported conducting a complete case analysis; almost all the remainder did not specify how they handled missing data in their analysis. Most RCTs reported neither on missing data separately for different outcomes nor addressed risk of bias associated with missing data. Very few RCTs described a mechanism of missingness (e.g., missing completely at random, missing not at random), and none of the 13 RCTs that imputed outcome took into account the uncertainty associated with imputing outcomes.

### 4.2. Strengths and limitations

"As stated in the protocol, this study focused on dichotomous outcome data, given the methodological and statistical issues vary substantively for continuous data" [8]. We have excluded time-to-event outcomes for the same reason. We have assessed the reporting and methods for handling missing participant data for continuous outcomes elsewhere [15].

To our knowledge, this is the largest methodological survey on missing data in RCTs and the first to specifically explore how RCT authors report on categories of participants that might have missing data. In addition, our sample of RCTs was not restricted to a specific health-related discipline, which increases the generalizability of our findings. We used systematic and transparent methods, pilot tested our data abstraction form, and conducted training and calibration exercises for review team members. The core team met on a weekly basis to resolve outstanding issues and conducted triplicate and independent data abstraction as needed to ensure the quality of the data.

### 4.3. Interpretation of findings

Although the median percentage of participants who were explicitly not followed-up was 5.8%, when adding those with unclear follow-up status, the total median percentage doubled to 11.7%. Although less extreme, our results are consistent with those of Marciniak et al., who reported that FDA-calculated loss to follow-up rates were consistently higher than the published rates (median 13% vs. 0.9%, respectively) [6]. Another way of looking at the data is to compare the median percentage of participants who were explicitly not followed-up (5.8%) with the median percentage of participants with unclear follow-up status (9.4%).

An important finding of this survey is that almost one-third of the RCTs did not mention any category of participants that might have with missing data. These RCTs either did not have missing data or failed to report the missing data they had. To the extent the latter is the case, results from our sample of RCTs that reported at least one category of participants that might have missing data ($n = 400$) may be conservative that is underestimating the real extent of missing data. Another important finding is the high percentage of RCTs not explicitly reporting on the follow-up status of participants (range 32−86%; Table 2). This poor reporting might explain, at least in part, why the majority of SRs fail to adequately report on and handle missing data [7,12,13,16−26].

A rough method to assess the extent of bias associated with missing data is to compare its rate with the risk difference for the outcome of interest. In their previously mentioned study, Marciniak et al. found that the risk difference in the included RCTs had a median of 1.0% (range, 0.2−3.0%) [6]. On the other hand, they found that the median of rates of missing data was 0.4% based on published information, and 13% based on information submitted for FDA review. Although the first median (0.4%) might suggest that the risk of bias associated with missing data is low, the second median (13%) suggests that the risk is actually high. The limitation of their analysis is the comparison of the median missing data rate across study to the median risk difference across studies.

In our study, we compared the risk difference to the missing data rate for each RCT by calculating their ratio. The ratio for participants that were either explicitly not followed-up or with unclear follow-up status had a median of 1.7, which implies that 50% of the RCTs have a ratio of 1.7 or larger. We interpret this that at least half of the RCTs have a high risk of bias associated with missing data. The ratio for participants that were explicitly not followed-up to the risk difference had a 75th percentile of 3.0, which implies that 25% of the RCTs have a ratio of 3 or larger. We interpret this as a substantive minority of RCTs having a high risk of bias associated with missing data. These findings are consistent with those of Marciniak et al. [6].

Additional evidence for the extent to which the missing data can affect the risk of bias comes from a previous study we conducted on the effect of missing data on RCT results [1] found that up to one-third of RCTs published in five top general medical journals lose significance when applying plausible assumptions about their loss to follow-up. In that study, rate of participants with missing data was 6%, implying that a much higher percentage of RCTs would likely lose significance when considering the 11.7% of RCT participants that were either explicitly not followed-up or with unclear follow-up status.

We found that complete case analysis was the most frequently reported method for handling missing data in the included RCTs. Although methodologist agrees on the use of complete case analysis to handle missing data in SRs [27], this is not the case when it comes to RCTs. Some methodologists consider that using complete case analysis

**Box 2.** Comparison of the findings of the most recent methods surveys assessing the reporting of missing data, its handling, and the assessment of the associated risk of bias

| Study | Sampling frame, *N* | Description of missing data | % of RCTs reporting missing data | % of participants with missing data | % of RCTs reporting on reasons for missing data |
|---|---|---|---|---|---|
| Current study | 100 SRs with statistically significant effect published in 2012; *N* = 638 | "19 categories of participants that might have missing data" | 63 (400 RCTs) | Median of 11.7% across the 400 RCTs with missing data | 100%, as study defined missing data based on reasons |
| Hussain 2017 [11] | Palliative care RCTs (January 2009 to April 2014); *N* = 108 | "Missing data" | 86 (93 RCTs) | 19% among all participants in the 93 RCTs with missing data | 71% of the 93 RCTs with missing data |
| Fielding 2016 [12] | Top four medical journals (50% random sample from 2013 to 2014 RCTs on quality of life); *N* = 87 | "Missing quality of life data" | 95 (83 RCTs) | Median is between 5% and 10%[a] | Not assessed |
| Bell 2014 [13] | Top four medical journals (July to December 2013 RCTs); *N* = 77 | "Some missing data" | 95 (73 RCTs) | Median of 9% in the 73 RCTs with missing data | 90% of the 73 RCTs with missing data |
| Powney 2014 [14] | 100 RCTs reporting on longitudinal or repeated measurements (2005–2012); *N* = 100 | "Missing data" | 91 (91 RCTs) | Not assessed | 38% of the 91 RCTs with missing data |
| Akl 2012 [1] | Top five medical journals (2008 RCTs reporting statistically significant effects); *N* = 235 | "Some loss to follow-up" | 81 (191 RCTs) | Median of 6% across the 191 RCTs with missing data | Not assessed |

*Abbreviations*: CCA, complete case analysis; missing data: missing data; RCTs, randomized controlled trials; SRs, systematic reviews.
[a] Excluding the studies with no missing data (5%) and studies where the proportion of missing data is unclear (35%).
[b] The primary analysis strategy for the quality of life outcome was a complete case analysis for 42 of 87 RCTs (48%).

may bias the estimate of RCT treatment effect [28], whereas others recommend this approach only when data are missing completely at random [29]. A recent simulation study showed that multiple imputations render less biased estimates than other methods including complete case analysis and worst-case scenario when analyzing binary alcohol clinical trial outcomes [30].

Many experts recommend dealing with missing data in RCTs taking into account the mechanism of missingness (e.g., missing completely at random and missing at random) [7,31–47]. We found that only 3 of 400 RCTs (<1%) reported on missingness mechanism. One potential explanation is that it might be challenging for RCT authors to judge the mechanism of missingness, which can vary across and even within categories of patients. As a consequence, it would not be feasible for SR authors to make imputations taking into account the mechanism of missingness.

### 4.4. Comparison with similar studies

Box 2 compares our findings to those of five recent methods surveys with similar objectives [1,11–14]. The percentage of RCTs with missing data varied across these six surveys, ranging from 63% to 95%. Similarly, the average percentage of participants with missing data per RCT ranged from 6% to 19%. One reason for these variabilities is the use of different sampling frames across surveys. For example, the survey of RCTs assessing missing quality of life data had the highest percentage of RCTs [12] and that conducted in the context of palliative care had the highest median of participants [11]. Another reason is the use of different definitions of missing data. For example, certain surveys accepted the definition of RCTs being assessed, whereas others used predefined categories of participants with missing data. Similarly, the percentage

| % of RCTs comparing baseline characteristics between patients with observed and missing outcomes | Most common method of handling missing data (%) | % of RCTs reporting on sensitivity analysis to assess the impact of missing data | % of RCTs reporting on missing data per outcome | % of RCTs reporting on mechanism of missing data | % of RCTs taking uncertainty into account when imputing outcomes |
|---|---|---|---|---|---|
| 2% of the 400 RCTs with missing data | CCA (55% in the 400 RCTs with missing data) | 5% of the 400 RCTs with missing data | 3% of the 400 RCTs with missing data | 3% of the 400 RCTs with missing data | 0% of the 13 RCTs that imputed outcomes for at least one category |
| 13% of the 93 RCTs with missing data | CCA (37% in the 93 RCTs with missing data) | 16% of the 93 RCTs with missing data | Not assessed | 3% in the 93 RCTs with missing data | Not assessed |
| Not assessed | CCA (67% in the 83 RCTs with missing data)[b] | 15% (this was based on the use of imputations) | Not assessed | 13% of the 83 RCTs with missing data | Not assessed |
| 12% of the 73 RCTs with missing data | CCA (45% in the 73 RCTs with missing data) | 35% of the 73 RCTs with missing data | Not assessed | Not assessed | Not assessed |
| Not assessed | CCA (35% in the 91 RCTs) | Not assessed | Not assessed | Not assessed | Not assessed |
| Not assessed | CCA (23% in the 191 RCTs with missing data) | Not assessed | Not assessed | Not assessed | Not assessed |

of RCTs reporting on the reasons for missingness varied across surveys. That is likely because of the differential consideration of certain categories as reasons for missingness (e.g., our survey, unlike others, we did not consider ''dead'' as equivalent to missing data). Only our survey assessed whether the RCTs reported on missing data per outcome.

The approach to handling missing data was relatively consistent across the surveys, with most RCTs implementing complete case analysis (35–55%). The percentage of RCTs reporting sensitivity analysis to assess the impact of missing data ranged from 5% to 35%. Only our survey assessed whether the RCTs took uncertainty into account when imputing outcomes, as suggested by a number of experts [29,44,48,49]. We found that only 13 of 400 RCTs that included participants with possible missing data reported imputing data. None of these 13 RCTs reported taking uncertainty into account.

### 4.5. Implications of findings

Existing guidance recommends that RCTs report the proportion, reasons, and mechanisms of missing data and how RCT authors accounted for them in the analysis and assessed the associated risk of bias [4,18,50]. These recommendations should be adopted by RCT authors and better implemented by journal editors. We suggest that RCT authors additionally report the number of participants with missing data for each outcome and by study arm [3].

For handling missing data in the main analysis, consistent with the suggestion by White et al., we recommend that RCT authors apply plausible assumptions about the outcomes of participants with missing data [51]. These assumptions might depend on (1) the question being examined by the RCT [1], (2) the population involved, (3) the nature of the intervention, and (4) the reason for missingness. Randomized controlled trial authors might need to make different assumptions for different categories of missing data in the same RCT [14,37]. In terms of assessing the risk of bias associated with missing data, we recommend performing sensitivity analyses to explore the robustness of the results based on the assumption made in the main analysis [51].

There is increasing guidance available to SR authors on handling missing data when synthesizing RCT results [27,37,41−43,45,47,52−54]. One proposal is to provide individual participant data or data sharing. The World Health Organization and the International Committee of Medical Journal Editors have highlighted the importance of sharing RCT data [55]. Its significance is related to universal prospective registration and public disclosure of results from all RCTs [55]. Unfortunately, a recent survey of RCTs published in the British Medical Journal and PLOS Medicine after the adoption of data sharing policies by these journals found that 17 out of 37 RCTs (46%) met criteria for data availability [56].

Both RCT authors and journals editors need to better address missing data in trials reports. Until reporting of missing data is more explicit and transparent, users of the medical literature should take into account potentially missing data in addition to definitley missing data.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2018.10.001.

## References

[1] Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. BMJ 2012;344:e2809.

[2] Rombach I, Rivero-Arias O, Gray AM, Jenkinson C, Burke O. The current practice of handling and reporting missing outcome data in eight widely used PROMs in RCT publications: a review of the current literature. Qual Life Res 2016;25:1613−23.

[3] Akl EA, Kahale LA, Ebrahim S, Alonso-Coello P, Schunemann HJ, Guyatt GH. Three challenges described for identifying participants with missing data in trials reports, and potential solutions suggested to systematic reviewers. J Clin Epidemiol 2016;76:147−54.

[4] National Research Council. The prevention and treatment of missing data in clinical trials. Washington, DC: National Academies Press; 2010.

[5] Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367:1355−60.

[6] Marciniak TA, Cherepanov V, Golukhova E, Kim MH, Serebruany V. Drug discontinuation and follow-up rates in oral antithrombotic trials. JAMA Intern Med 2016;176(2):257−9.

[7] Gewandter JS, McDermott MP, McKeown A, Smith SM, Williams MR, Hunsinger M, et al. Reporting of missing data and methods used to accommodate them in recent analgesic clinical trials: ACTTION systematic review and recommendations. Pain 2014;155(9):1871−7.

[8] Akl EA, Kahale LA, Agarwal A, Al-Matari N, Ebrahim S, Alexander PE, et al. Impact of missing participant data for dichotomous outcomes on pooled effect estimates in systematic reviews: a protocol for a methodological study. Syst Rev 2014;3:137.

[9] Kahale LA, Diab B, Brignardello-Petersen R, Agarwal A, Mustafa RA, Kwong J, et al. Systematic reviews do not adequately report, or address missing outcome data in their analyses: a methodological survey. J Clin Epidemiol 2018;99:14−23.

[10] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377−81.

[11] Hussain JA, Bland M, Langan D, Johnson MJ, Currow DC, White IR. Quality of missing data reporting and handling in palliative care trials demonstrates that further development of the CONSORT statement is required: a systematic review. J Clin Epidemiol 2017;88:81−91.

[12] Fielding S, Ogbuagu A, Sivasubramaniam S, MacLennan G, Ramsay CR. Reporting and dealing with missing quality of life data in RCTs: has the picture changed in the last decade? Qual Life Res 2016;25:2977−83.

[13] Bell ML, Fiero M, Horton NJ, Hsu CH. Handling missing data in RCTs; a review of the top medical journals. BMC Med Res Methodol 2014;14:118.

[14] Powney M, Williamson P, Kirkham J, Kolamunnage-Dona R. A review of the handling of missing longitudinal outcome data in clinical trials. Trials 2014;15(1):237.

[15] Zhang Y, Florez ID, Colunga Lozano LE, Aloweni FAB, Kennedy SA, Li A, et al. A systematic survey on reporting and methods for handling missing participant data for continuous outcomes in randomized controlled trials. J Clin Epidemiol 2017;88:57−66.

[16] Hussain JA, White IR, Langan D, Johnson MJ, Currow DC, Torgerson D, et al. Missing data in randomised controlled trials evaluating palliative interventions: a systematic review and meta-analysis. Lancet 2016;387:S53.

[17] Adewuyi TE, MacLennan G, Cook JA. Non-compliance with randomised allocation and missing outcome data in randomised controlled trials evaluating surgical interventions: a systematic review. BMC Res Notes 2015;8:403.

[18] Akl EA, Shawwa K, Kahale LA, Agoritsas T, Brignardello-Petersen R, Busse JW, et al. Reporting missing participant data in randomised trials: systematic survey of the methodological literature and a proposed guide. BMJ Open 2015;5(12):e008431.

[19] Fielding S, Maclennan G, Cook JA, Ramsay CR. A review of RCTs in four medical journals to assess the use of imputation to overcome missing data in quality of life outcomes. Trials 2008;9:51.

[20] Fiero MH, Huang S, Oren E, Bell ML. Statistical analysis and handling of missing data in cluster randomized trials: a systematic review. Trials 2016;17:72.

[21] Karlson CW, Rapoff MA. Attrition in randomized controlled trials for pediatric chronic conditions. J Pediatr Psychol 2009;34(7):782−93.

[22] Masconi KL, Matsha TE, Echouffo-Tcheugui JB, Erasmus RT, Kengne AP. Reporting and handling of missing data in predictive research for prevalent undiagnosed type 2 diabetes mellitus: a systematic review. EPMA J 2015;6(1):7.

[23] Spineli LM. Missing binary data extraction challenges from Cochrane reviews in mental health and Campbell reviews with implications for empirical research. Res Synth Methods 2017;8(4):514−25.

[24] Wahlbeck K, Tuunainen A, Ahokas A, Leucht S. Dropout rates in randomised antipsychotic drug trials. Psychopharmacology 2001;155(3):230−3.

[25] Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin Trials 2004;1:368−76.
[26] Ibrahim F, Tom BD, Scott DL, Prevost AT. A systematic review of randomised controlled trials in rheumatoid arthritis: the reporting and handling of missing data in composite outcomes. Trials 2016;17(1):272.
[27] Akl EA, Kahale LA, Agoritsas T, Brignardello-Petersen R, Busse JW, Carrasco-Labra A, et al. Handling trial participants with missing outcome data when conducting a meta-analysis: a systematic survey of proposed approaches. Syst Rev 2015;4:98.
[28] Groenwold RH, Moons KG, Vandenbroucke JP. Randomized trials with missing outcome data: how to analyze and what to report. CMAJ 2014;186(15):1153−7.
[29] Little RJ, Rubin DBIn: Statistical analysis with missing data, 333. New York: John Wiley & Sons; 2014.
[30] Hallgren KA, Witkiewitz K, Kranzler HR, Falk DE, Litten RZ, O'malley SS, et al. Missing data in alcohol clinical trials with binary outcomes. Alcohol Clin Exp Res 2016;40(7):1548−57.
[31] Barnes SA, Mallinckrodt CH, Lindborg SR, Carter MK. The impact of missing data and how it is handled on the rate of false-positive results in drug development. Pharm Stat 2008; 7(3):215−25.
[32] Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. Stat Methods Med Res 2014;23(5):440−59.
[33] Bell ML, Kenward MG, Fairclough DL, Horton NJ. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ 2013;346:e8668.
[34] Buehl W, Heinzl H, Mittlboeck M, Findl O. Statistical problems caused by missing data resulting from neodymium:YAG laser capsulotomies in long-term posterior capsule opacification studies: problem identification and possible solutions. J Cataract Refract Surg 2008;34:268−73.
[35] Fielding S, Fayers P, Ramsay C. Predicting missing quality of life data that were later recovered: an empirical comparison of approaches. Clin Trials 2010;7:333−42.
[36] Fielding S, Fayers PM, Ramsay CR. Investigating the missing data mechanism in quality of life outcomes: a comparison of approaches. Health Qual Life Outcomes 2009;7:57.
[37] Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008; 5:225−39.
[38] Ibrahim JG, Chu H, Chen MH. Missing data in clinical studies: issues and methods. J Clin Oncol 2012;30:3297−303.
[39] Jorgensen AW, Lundstrom LH, Wetterslev J, Astrup A, Gotzsche PC. Comparison of results from different imputation techniques for missing data from an anti-obesity drug trial. PLoS One 2014;9:e111964.
[40] Liu M, Wei L, Zhang J. Review of guidelines and literature for handling missing data in longitudinal clinical trials with a case study. Pharm Stat 2006;5(1):7−18.
[41] Mavridis D, Chaimani A, Efthimiou O, Leucht S, Salanti G. Addressing missing outcome data in meta-analysis. Evid Based Ment Health 2014;17(3):85−9.
[42] Mavridis D, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Stat Med 2015;34:721−41.
[43] Spineli LM, Higgins JP, Cipriani A, Leucht S, Salanti G. Evaluating the impact of imputations for missing participant outcome data in a network meta-analysis. Clin Trials 2013;10:378−88.
[44] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.
[45] White IR, Higgins JP, Wood AM. Allowing for uncertainty due to missing data in meta-analysis–part 1: two-stage methods. Stat Med 2008;27:711−27.
[46] White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40.
[47] White IR, Welton NJ, Wood AM, Ades AE, Higgins JP. Allowing for uncertainty due to missing data in meta-analysis–part 2: hierarchical models. Stat Med 2008;27:728−45.
[48] Harel O, Mitchell EM, Perkins NJ, Cole SR, Tchetgen Tchetgen EJ, Sun B, et al. Multiple imputation for incomplete data in epidemiologic studies. Am J Epidemiol 2018;187:576−84.
[49] Rubin DBIn: Multiple imputation for nonresponse in surveys, 81. New York: John Wiley & Sons; 2004.
[50] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux P, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
[51] White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. Clin Trials 2012;9: 396−407.
[52] Akl EA, Johnston BC, Alonso-Coello P, Neumann I, Ebrahim S, Briel M, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. PLoS One 2013;8:e57132.
[53] Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions version 5.1.0 2011: The Cochrane Collaboration. Available at www.handbook.cochrane.org.
[54] Turner NL, Dias S, Ades AE, Welton NJ. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;34:2062−80.
[55] Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal. Ann Intern Med 2017;167:63−5.
[56] Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in the BMJ and PLOS Medicine. BMJ 2018;360:k400.