Journal of Clinical Epidemiology 115 (2019) 55–63

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

A guidance was developed to identify participants with missing outcome data in randomized controlled trials

Lara A. Kahale[a,b], Gordon H. Guyatt[c,d], Thomas Agoritsas[c,e], Matthias Briel[c,f], Jason W. Busse[c,g,h,i], Alonso Carrasco-Labra[c,j], Assem M. Khamis[a], Yuqing Zhang[c], Lotty Hooft[b,k], Rob J.P.M. Scholten[b,k], Elie A. Akl[a,c,*]

[a]*Clinical Research Institute, American University of Beirut, Beirut, Lebanon*
[b]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[c]*Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada*
[d]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada*
[e]*Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland*
[f]*Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University of Basel and University Hospital Basel, Switzerland*
[g]*Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada*
[h]*The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario, Canada*
[i]*The Michael G. DeGroote Centre for Medicinal Cannabis Research, McMaster University, Hamilton, Ontario, Canada*
[j]*Center for Evidence-Based Dentistry, Science Institute, American Dental Association, Chicago, IL, USA*
[k]*Cochrane Netherlands, University Medical Center Utrecht, Utrecht, The Netherlands*

Accepted 4 July 2019; Published online 9 July 2019

Abstract

Background and Objectives: In order for authors of systematic reviews to address missing data in randomized controlled trials (RCTs), they need to first identify the number of trial participants with missing data. The objective of this study was to provide guidance for authors of systematic reviews on how to identify participants with missing outcome data in reports of RCTs.

Methods: Guidance statements were informed by a review of studies addressing the topic of missing data and an iterative process of feedback and refinement, through meetings involving experts in health research methodology and authors of systematic reviews.

Results: The proposed guidance includes (1) definitions of key terms, (2) 19 categories of participants described in RCT reports and who might have missing data, and (3) a flowchart on how to judge the outcome data missingness for each category. The judgment of missingness relies on how trial authors report on the categories and handle them in their analyses. Practically, for their primary analysis, systematic review authors should choose how to identify participants with missing outcome data (i.e., use either ''definitely missing data'' or ''total possible missing data''), then select a method for handling missing data in meta-analysis. Sensitivity analyses should be undertaken to explore consistency with competing options for classifying patients as having missing data.

Conclusion: Adopting the proposed guidance will help promote transparency and consistency regarding how missing data are managed in systematic reviews.

Keywords: Missing data; Systematic reviews; Meta-analysis; Randomized controlled trials; Risk of bias; Guidance

Funding: This paper is part of a project on addressing missing trial participant data in systematic reviews funded by the Cochrane Methods Innovation Fund. The funder was not involved in study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication. The researchers are independent from the funder and had full access to all the data.

Conflicts of interest: All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. They declare being involved in previous publications making recommendations on the topic missing data.

* Corresponding author. Department of Internal Medicine, American University of Beirut Medical Center, P.O. Box: 11-0236; Riad-El-Solh Beirut 1107 2020, Beirut, Lebanon. Tel.: +00961 1 350000; fax: +00961 1 374374.

E-mail address: ea32@aub.edu.lb (E.A. Akl).

https://doi.org/10.1016/j.jclinepi.2019.07.003

What is new?

Key findings

- Authors of systematic reviews face a number of challenges when trying to identify the number of trial participants with missing data.
- We propose a guidance for authors of systematic reviews on how to identify participants with missing outcome data in reports of randomized controlled trials.

What this adds to what was known?

- The judgment of missingness relies on how trial authors report on categories of participants and handle them in their analyses.
- The guidance classifies participants as having either "definitely missing data" or "potentially missing data."

What is the implication and what should change now?

- This guidance fits into a larger one that includes first requesting missing data by outcome from trial authors and eventually assessing the associated risk of bias using Grading of Recommendations Assessment, Development and Evaluation.

Box 1 Three main challenges faced by authors of systematic reviews when identifying missing outcome data [3]

1. Although systematic reviewers require information about missing data to be reported by outcome, trialists typically report the information by participant;
2. It is not always clear whether trialists have successfully followed participants in certain categories (e.g., those who withdrew consent); that is, whether some categories of participants did or did not have missing data;
3. It is not always clear how the trialists dealt with missing data in their analyses.

1. Introduction

Authors of systematic reviews are frequently confronted with missing data for one or more outcomes of trial participants. Recent studies found that 42% of systematic reviews [1] and 63% of randomized controlled trials (RCTs) reported on participants with missing data [2]. Missing data may bias results of RCTs when outcomes of those missing differ systematically from those who have been followed. Thus, inferences from reviews of RCTs may be misleading if trial authors do not handle missing data appropriately [3–5].

Guidance for authors of systematic reviews on how to assess the risk of bias associated with missing data in a meta-analysis and how to handle this is available for both dichotomous and continuous outcomes [6–14]. However, to follow this guidance, they first need to identify for every outcome how many trial participants actually have missing data. This task can become quite complex, if RCTs do not clearly report this information.

Identifying missing outcome data in trial reports is associated with three main challenges (see Box 1) [3].

As an example of unclear reporting, RCTs do not always specify whether participants categorized as "lost to follow-up" actually developed an event for the outcome of interest before they were lost to follow-up. Although systematic reviewers typically consider participants lost to follow-up as having missing data for all outcomes, this may not be the case [3]. Ideally, RCTs should report missing data by outcome, but very few RCTs do so; a methodologic survey of 638 RCTs found that 0.7% reported missing data by outcome [2]. Many RCTs do not report the method(s) used for handling missing data (43% as a conservative estimate) [2].

Some trialists might assume that participants with missing data experienced an event for the outcome of interest and include them in the numerator (number of events for that outcome), but without specifying this approach. This is a standard approach in tobacco cessation trials. According to Russell standards, participants who are analyzed are counted as smokers if their smoking status at final follow-up cannot be determined [15,16]. Indeed, Foulds et al. telephoned participants who were lost to follow-up in a hospital-based smoking cessation trial and reported that 100% of these participants relapsed [17,18]. Similarly, in mental health research, many experts observed that missing data are likely not to be missing at random (i.e., the probability that an observation is missing depends on the unseen observations themselves); assuming that they developed an event for the outcome of interest is very plausible [19,20]. If trialists have already included events for some of those they report to have missing data, and review authors assume that participants with missing data had an event for the outcome of interest, the result will be double counting [3].

The extent of missing data in RCTs might be larger than what authors explicitly report. For example, one study compared "loss to follow-up rates" in published reports of RCTs of oral antithrombotic agents with loss to follow-up rates derived from more detailed documents made available to the FDA for the same RCTs [21]. They found a large discrepancy between the median published rate of all "missing follow-up categories" (0.9%) and the median of the FDA-calculated loss to follow-up rates (13%). We found similar results in a recently published

review of 638 RCTs; specifically, the median percentage of participants who were explicitly not followed-up was 5.8%, but this increased to 11.7% when considering patients for whom the follow-up status was unclear [2].

Given the aforementioned challenges, and until reporting of missing data becomes more explicit, authors of systematic reviews require guidance on how to identify participants with missing outcome data in RCT reports. We are not aware of any such existing guidance. In particular, the recent update of the Cochrane handbook does not address the issue [14].

2. Objective

The objective of this study was to provide guidance for authors of systematic reviews on how to identify participants with missing outcome data in reports of RCTs.

3. Methods

To inform our guidance, we reviewed the following studies on the topic of missing data:

- Proposed approaches for reporting and handling missing data in RCTs [22] and in systematic reviews [23,24];
- Conceptual paper on challenges faced by systematic reviewers while identifying trial participants with missing data [3];
- Methodological surveys on the reporting and handling of missing data in RCTs [2,25] and systematic reviews [1,26];
- Impact of missing data on effect estimates in RCTs [27];
- Impact of missing data on effect estimates in systematic reviews (unpublished data);
- Guidance for handling missing data of dichotomous [6] and continuous outcomes in systematic reviews [7,28];
- Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance for assessing risk of bias associated with missing data in a body of evidence [8].

Accordingly, we developed a draft guidance for authors of systematic reviews on how to identify participants with missing outcome data in reports of RCTs. Then, we revised guidance using an iterative process of feedback and refinement through three face-to-face meetings and several teleconferences involving experts in health research methodology, and authors of systematic reviews as the end users. In addition, we conducted two workshops at Cochrane colloquia for further feedback.

This guidance is for meta-analyses of group-level data from RCTs. It does not address methods for meta-analyses of individual participant data.

4. Results

We describe below the proposed guidance for identifying missing outcome data which includes the following: (1) the definitions of key terms, (2) the categories of participants described in RCT reports that might be associated with missing data, and (3) how to judge the outcome data missingness for these categories.

4.1. Definitions

We used the following definitions (see Fig. 1):

Missing data: outcome data from included RCTs that are not available to the authors of systematic reviews, whether from published RCT reports or through contact with trialists.
Definitely missing data: participants clearly have missing outcome data based on the RCT reporting.
Potentially missing data: participants potentially have missing outcome data, but it is not explicitly reported in the RCT report.
Total possible missing data: participants who either have definitely or potentially missing outcome data.

4.2. Categories

We developed a draft taxonomy of categories of participants described in RCT reports and who might have missing data. We refined this taxonomy iteratively through its application to data extraction in a succession of published studies: 235 RCTs [27], 202 systematic reviews [6], 100 systematic reviews [1], 200 RCTs [25], and 638 RCTs [2] (for a total of 1,073 RCTs and 302 systematic reviews). We labeled categories to reflect wording used in RCT reports, that is, the presentation that systematic review authors actually face: we are not suggesting using these categories when reporting RCTs. Table 1 lists the 19 final categories of participants that might have missing data along with their description.

We considered two additional categories reported in trials (“dead” and “excluded as part of center exclusion”) but decided not to consider them as missing data as explained here:

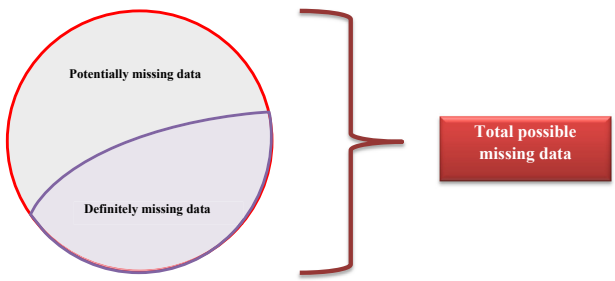

Fig. 1. Definitions of missing data.

Table 1. Categories of participants described in RCT reports who might have missing data

Category of participants that might have missing data	Description of the category
Explained lost to follow-up	Participants described as lost to follow-up, and trialists provided an explanation, e.g., relocated to a different country
Unexplained lost to follow-up	Participants described as lost to follow-up, and trialists did not provide an explanation
Outcome not assessable	Data of a certain outcome for a number of participants are not available because the outcome adjudicators could not assess their outcome. For example, venography could not be done for a number of participants
Data not available	Participants are still part of the RCT; however, due to incomplete or missing record, the outcome data of these participants are missing
Ineligible or mistakenly randomized	Participants who, subsequent to randomization, are either found not to have the condition of interest (e.g., are not pregnant in an RCT among pregnant women) or did not undergo a procedure for which the intervention is intended (e.g., did not undergo surgery in an RCT of postoperative thromboprophylaxis)
Did not receive first dose/treatment	Participants who did not receive the ''first dose'' of the intervention to which they were randomized
Ineligible due to early occurrence of outcome	Participants who were eligible at baseline then developed the outcome of interest soon after enrollment. These are considered ineligible if the trialists judge that the occurrence of the outcome cannot be related to the intervention of interest
Experienced adverse events	Participants who developed adverse events but without clear indication whether or not they discontinued the RCT
Noncompliant	Participants who were nonadherent or otherwise violated the protocol
Crossover	Participants randomized to one arm, but who received the intervention meant for another treatment arm
Withdrew consent	Participants who withdraw their consent to participate in the RCT
Discontinued due to adverse events	Participants who discontinued the RCT due to adverse events
Discontinued trial prematurely	Participants who left the RCT but for whom a reason for discontinuation was not provided
Withdrawn by investigator/clinician	Participants who left the RCT through a decision made by the investigator or clinician (e.g., due to medical necessity)
Unintended protocol violation	Participants who left the RCT due a protocol violation for which they are not responsible (e.g., unavailability of hospital beds)
Lack of efficacy	Participants who left the RCT because they perceived no benefits from the intervention they were randomized to
Protocol violation by investigator/clinician	Investigator/clinician violated the protocol (e.g., change the intended intervention) due to a medical reason
More than one category reported together	The number refers to participants belonging to two or more of the aforementioned categories
Other	Reason different from the above

Abbreviations: RCT, randomized controlled trial.

''Dead'' category: As ''death'' is a competing outcome, we consider that participants described as ''dead'' to not have missing data. In other words, the interpretation of the outcome of interest should consider these participants as ''dead,'' and not as having missing data. See Box 2 for example.

''Excluded as part of center exclusion'' category: In multicenter trials, individual centers may be excluded from the study due to a specific reason (e.g., low recruitment, nonadherence to trial protocol). Participants, who have been already enrolled by those centers before the decision of exclusion, will be excluded from the study and not followed up. We consider participants belonging to this category to not have missing data and to be appropriately excluded from the denominator of trial participants.

4.3. Judging outcome data missingness

Fig. 2 shows the flowchart illustrating our proposed guidance on how authors of systematic reviews could judge the missingness of outcome data in RCT reports.

''Dead'': As noted earlier, we consider participants belonging to this category to definitely not have missing data.

''Excluded as part of center exclusion'': As noted earlier, we consider participants belonging to this category to definitely not have missing data.

For the first four categories in Table 1 (''explained lost to follow-up,'' ''unexplained lost to follow-up,'' ''outcome not assessable,'' or ''data not available''),

Box 2 Death as a competing outcome

A competing risk is an event that either prevents the observation of an event of interest or modifies the chance that this event occurs [29]. Consider an RCT comparing a palliative care intervention to standard of care, showing an increased incidence of death but improved quality of life among those who survive. When analyzing the results for the quality of life outcome, one should not impute data for those who died before their quality of life could be assessed at the end of the RCT.

Abbreviations: RCT, randomized controlled trial.

we consider participants belonging to these categories to definitely have missing data.

For the remaining 15 categories, the guidance for the remaining categories is based on the reporting of the trialist on the following:

1. How the RCT reported on the follow-up status for each category;
2. How the RCT handled each category.

Based on these two criteria, authors of systematic reviews can judge whether participants belonging to each specific category have (1) definitely missing data; (2); potentially missing data; or (3) definitely not missing data.

If trialists explicitly reported that these participants were followed up, then systematic review authors should count them as definitely not having missing data. If trialists explicitly reported that participants were not followed up, then systematic review authors should count them as definitely having missing data.

When trial authors do not explicitly report follow-up status—the case in 45% of RCTs [2]—systematic review authors should check how authors handled these categories. If such participants were excluded from the trial analysis (i.e., excluded from the denominator [and numerator]), then the reviewers should consider them definitely missing. Participants for whom the trialists imputed outcomes could be considered as having definitely missing data. However, the

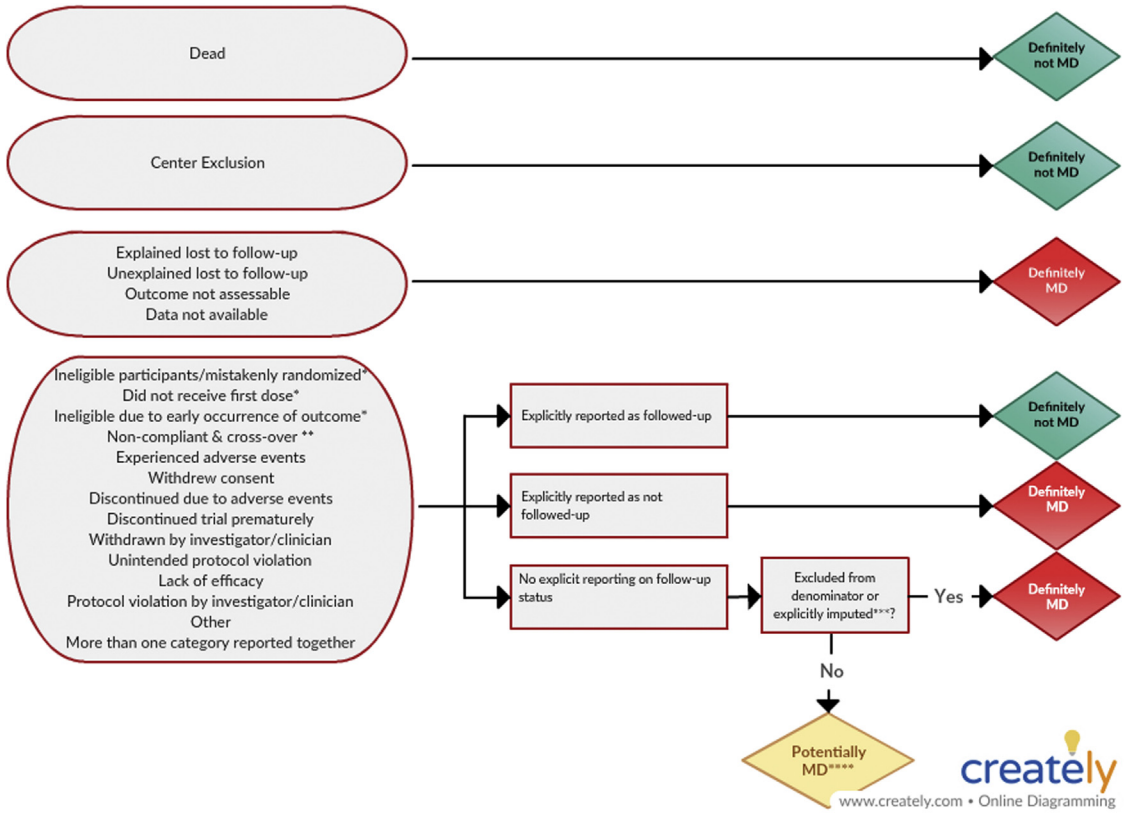

Fig. 2. How authors of systematic reviews could judge the missingness of outcome data in reports of randomized controlled trials. *Participants belonging to these categories not meeting the conditions for appropriate exclusion (see text). **When both intention-to-treat analysis and per-protocol analysis are reported, assume that participants belonging to the categories are followed up and consequently do not have missing data. ***Participants for whom the trialists-imputed outcomes could be considered as having definitely missing data. However, the systematic reviewers should not treat them as missing data unless it is possible to obtain the number of observed/actual events (i.e., excluding imputed events) to avoid double counting. ****When follow-up status is not explicitly reported in the RCT report, assume that they were followed up and consequently do not have missing data. *Abbreviations:* FU, follow-up; MD, missing data.

systematic reviewers should not treat them as missing data unless it is possible to obtain the number of observed/actual events (i.e., excluding imputed events) to avoid double counting. If it was unclear how primary study investigators handled participants with unclear follow-up status—the case in 52% of RCTs [2]—then it would be best to count them as potentially missing data.

Besides common situation mentioned in Table 1, we propose specific considerations for the following situations:

Participants who are ''ineligible or mistakenly randomized'' may be considered as appropriately excluded by the trialists if information about ineligibility was available at randomization and those making the decision regarding exclusion were blind to allocation [30]. Similarly, those who ''did not receive first dose/treatment'' or who are ''ineligible due to early occurrence of outcome'' may be considered as appropriately excluded by the trialists. Under these conditions, systematic review authors should not count such participants as having missing data. However, if either of these two conditions is not satisfied, the exclusion is considered inappropriate and these participants might have missing data, depending on how trialists report on their follow-up status.

''Experienced adverse events'': when follow-up status of participants belonging to this category is not explicitly reported, we suggest that systematic review authors assume that they were followed up and consequently do not have missing data.

5. Discussion

5.1. Summary

We present guidance for authors of systematic reviews on how to identify (and classify) participants with missing outcome data in reports of RCTs and how to deal with presentations or descriptions that leave uncertainty as to the number of patients with missing data. Our approach uses categories of participants described in RCT reports, and who might have missing data, and relies on how trial authors report on those categories and handle them in their analyses (Table 2).

The guidance proposed in this study complements existing guidance on handling and assessing risk of bias associated with missing data [6–14,31–34]; however, for their primary analysis, systematic reviewers must choose between two options: use either ''definitely missing data'' or ''total possible missing data.'' Review authors also need to choose a method for handling missing data in the meta-analysis [6]. To test the robustness of the analysis that follows from these choices, the authors could explore sensitivity analyses using alternatives for identifying participants with missing outcome data and for handling missing data. Using the ''total possible missing data'' (compared with using ''definitely missing data'') in the primary analysis will yield a less precise pooled effect that is also less robust when subjected to sensitivity analyses. The main advantage of using the ''total possible missing data'' (compared with using ''definitely missing data'') is increased confidence in the results if the pooled effect estimate is found to be robust.

Table 2. Judging of outcome data missingness based on the reporting and handling in the trial of categories of participants that might have missing data

Judging of outcome data missingness	Categories of participants that might have missing data
Definitely not missing data	• Participants explicitly reported as followed up • Participants who died during the trial • Participants belonging to centers that were excluded

Definitely missing data	• Participants explicitly reported as not followed up;
	• Participants with unclear follow-up status and
	  • excluded from the denominator of the analysis (i.e., complete case analysis), or
	  • included in the denominator of the analysis and their outcomes were explicitly stated to be imputed. However, the systematic reviewers should not treat them as missing data unless it is possible to obtain the number of observed/actual events (i.e., excluding imputed events) to avoid double counting.

Potentially missing data	• Participants with unclear follow-up status (e.g., included in the denominator of the analysis and their outcomes were not explicitly stated to be imputed)
Total possibly missing data	• Participants who have either definite or potential missing data

5.2. Strengths and limitations

To our knowledge, this is the first guidance for systematic review authors on how to identify participants with missing outcome data in reports of RCTs. The guidance is structured, transparent, and hopefully easy to implement. We labeled the categories to reflect and capture the wording used in RCT reports with which systematic review authors have to deal. We built the guidance based on extensive methodological work on the topic of missing data. We refined our recommendations using an iterative process

during which we applied the categorization of participants who might have missing data to samples of RCTs and systematic reviews (a total of 1,073 RCTs and 302 systematic reviews).

One limitation is that our proposed approach to judging of data missingness did not benefit from as much validation as did the categorization of participants who might have missing data. However, our approach to judging of data missingness is consensus based and builds on the relevant data on the subject by Marciniak et al. [21]. 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 [21]. 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.

5.3. The broader approach to addressing missing data

A broader approach to addressing missing data in trials includes (in addition to identifying and handling missing data) the avoidance and better reporting of missing data, as well as sharing individual participant data. Indeed, the best way to address missing data in RCTs is to minimize the extent of—if not avoid—missing data. Many strategies have been suggested to improve retention in RCTs (e.g., monetary incentives) [35–38]. Similarly, trial methodologists have proposed strategies to improve the reporting of missing data (see Box 3) [3,22,39,40].

If trial authors make individual participant data of their RCTs publicly available, systematic review authors will no longer need to make judgments on the extent of missing data of participants. Both the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) have emphasized the importance of sharing RCT data [41,42]. However, a recent survey of RCTs published in the *BMJ* and *PLOS Medicine* subsequent to the adoption of data-sharing policies by these journals found that less than 50% of RCTs met criteria for data availability [41].

Improved reporting of group-level data can facilitate the handling of missing data in meta-analyses. Ideally, trialists would report, in a standardized data file compatible with meta-analysis software, the number of participants randomized, the number of participants with missing data, and the number of events for each outcome. We acknowledge that trialists are limited by word count in their journal publications, and that such information may appear in an appendix.

Box 3 Proposed approaches for reporting missing data

- Report methods used to prevent missing data;
- Report number of participants with missing data for each outcome, by study arm, and by time frame if relevant;
- Report rates of missing data by trial arms;
- Report a flow diagram of participants;
- Report any differences between baseline characteristics of participants with and without missing data;
- Report the reasons for missing data (refrain from reporting more than one category lumped together and ''other'' category as they create further confusion and uncertainty);
- Report method(s) for handling missing data in analysis;
- Report results of any sensitivity analyses to assess the associated risk of bias;
- Discuss implication of missing data on interpreting the results.

5.4. Implication for practice

As authors of systematic reviews will always face missing data in trials included in meta-analyses, we suggest the following stepwise approach to deal with missing data:

1. If trialists fail to provide the data in their trial report, request missing data by outcome and information on how they dealt with them in the analysis;
2. If the trialists do not provide sufficient information, follow the guidance suggested in this paper to identify participants who have either definitely or potentially missing data;
3. Assess risk of bias associated with missing data trial following GRADE guidance [8];
4. Report on all the aforementioned steps.

5.5. Implications for future research

Because this guidance has not been validated yet, it would be optimal to verify whether the categories judged to actually have missing data, for example, by comparing reported group-level data with individual participant data. Ultimately, the comparison of the approach against individual patient data would secure the validity of the approach.

Acknowledgments

Authors' contributions: L.A.K., G.H.G., and E.A.A. contributed to the conception and design of the article, data analysis, interpretation of data, and drafting the article. T.A., M.B., J.W.B., A.C.-L., A.M.K., Y.Z., L.H., and R.J.P.M.S. contributed to the critical revision of the article for important intellectual content. All authors reviewed and approved the final version.

References

[1] 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.

[2] Kahale LA, Diab B, Khamis AM, Chang Y, Lopes LC, Agarwal A, et al. Potentially missing data was considerably more frequent than definitely missing data in randomized controlled trials: a methodological survey. J Clin Epidemiol 2018;106:18−31.

[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] 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.

[5] 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.

[6] 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.

[7] Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, et al. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol 2013;66:1014−1021 e1.

[8] Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. J Clin Epidemiol 2017;87:14−22.

[9] Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008;5:225−39.

[10] 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.

[11] 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.

[12] 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.

[13] 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.

[14] Higgins JP, Surace J, Page MJ, Sterne JAC. Chapter 8: assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch V, editors. Draft version (16 September 2018) for inclusion, Cochrane Handbook for Systematic Reviews of Interventions. London: The Cochrane Collaboration; 2018.

[15] Hajek P, West R. Commentary on Smolkowski et al.(2010): why is it important to assume that non-responders in tobacco cessation trials have relapsed? Addiction 2010;105(6):1016−7.

[16] West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005;100(3):299−303.

[17] Foulds J, Stapleton J, Hayward M, Russell MA, Feyerabend C, Fleming T, et al. Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital: a placebo-controlled trial. Arch Fam Med 1993;2(4):417−23.

[18] Jackson D, White IR, Mason D, Sutton S. A general method for handling missing binary outcome data in randomized controlled trials. Addiction 2014;109(12):1986−93.

[19] 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.

[20] Mavridis D, White IR. Dealing with missing outcome data in meta-analysis. Res Synth Methods 2019;10(2). https://doi.org/10.1002/jrsm.1349.

[21] 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.

[22] 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.

[23] 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.

[24] Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Flórez ID, Pichika SC, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials. J Clin Epidemiol 2017;88:67−80.

[25] 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.

[26] Akl EA, Carrasco-Labra A, Brignardello-Petersen R, Neumann I, Johnston BC, Sun X, et al. Reporting, handling and assessing the risk of bias associated with missing participant data in systematic reviews: a methodological survey. BMJ Open 2015;5(9):e009368.

[27] 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.

[28] Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol 2014;67:560−70.

[29] Noordzij M, Leffondré K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant 2013;28(11):2670−7.

[30] Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325(7365):652.

[31] 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.

[32] 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.

[33] Altman DG. Missing outcomes in randomized trials: addressing the dilemma. Open Med 2009;3(2):e51−3.

[34] Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials−a practical guide with flowcharts. BMC Med Res Methodol 2017;17:162.

[35] Brueton VC, Tierney J, Stenning S, Harding S, Meredith S, Nazareth I, et al. Strategies to improve retention in randomised trials. Cochrane Database Syst Rev 2013;2:MR000013.

[36] Dziura JD, Post LA, Zhao Q, Fu Z, Peduzzi P. Strategies for dealing with missing data in clinical trials: from design to analysis. Yale J Biol Med 2013;86(3):343−58.

[37] Hollestein L, Carpenter J. Missing data in clinical research: an integrated approach. Br J Dermatol 2017;177(6):1463−5.

[38] Little R, Cohen M, Dickersin K, Emerson S, Farrar J, Neaton J, et al. The design and conduct of clinical trials to limit missing data. Stat Med 2012;31:3433−43.

[39] 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.

[40] National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Washington (DC): The National Academic Press; 2010.

[41] 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.

[42] 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 Editors. Ann Intern Med 2017; 167:63−5.