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GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence

Gordon H. Guyatt[a,b], Shanil Ebrahim[a,c], Pablo Alonso-Coello[a,d], Bradley C. Johnston[a,c,e,f], Alexander G. Mathioudakis[d], Matthias Briel[a,g], Reem A. Mustafa[a,h], Xin Sun[i], Stephen D. Walter[a], Diane Heels-Ansdell[a], Ignacio Neumann[j], Lara A. Kahale[k], Alfonso Iorio[a,b], Joerg Meerpohl[l,m], Holger J. Schünemann[a,b], Elie A. Akl[a,k,*]

[a]*Department of Health Research Methods, Evidence and Impact, McMaster University, 1200 Main St. West, Hamilton L8S 4K1, Canada*
[b]*Department of Medicine, McMaster University, 1200 Main St. West, Hamilton L8S 4K1, Canada*
[c]*Systematic Overviews through Advancing Research Technology (SORT), Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, 555 University Ave, Toronto, ON M5G 1X8, Canada*
[d]*Iberoamerican Cochrane Centre, CIBERESP-IIB Sant Pau, Casa de Convalescéncia, 4 th floor, C. Sant Antoni Maria Claret 171, Barcelona 08041, Spain*
[e]*Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON M5G 1X8, Canada*
[f]*Institute for Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, 155 College St, Toronto, ON M5T 3M7, Canada*
[g]*Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Hebelstrasse 10, Basel 4056, Switzerland*
[h]*Department of Internal Medicine, Kansas University Medical Center, 3901 Rainbow Blvd, Kansas City, KS MS3002, USA*
[i]*Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, China*
[j]*Department of Internal Medicine, Pontificia Universidad Catolica de Chile, Av Libertador Bernardo O'Higgins 340, Santiago, Región Metropolitana, Chile*
[k]*Department of Internal Medicine, American University of Beirut, Riad-El-Solh Beirut, Beirut 1107 2020, Lebanon*
[l]*Cochrane Germany, Medical Center–University of Freiburg, Breisacher Strasse 153, Freiburg 79110, Germany*
[m]*Centre de Recherche Épidémiologie et Statistique Sorbonne Paris Cité–U1153, Inserm/Université Paris Descartes, Cochrane France, Hôpital Hôtel-Dieu, 1 place du Parvis Notre Dame, Paris Cedex 04 75181, France*

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Abstract

Objective: To provide GRADE guidance for assessing risk of bias across an entire body of evidence consequent on missing data for systematic reviews of both binary and continuous outcomes.

Study Design and Setting: Systematic survey of published methodological research, iterative discussions, testing in systematic reviews, and feedback from the GRADE Working Group.

Results: Approaches begin with a primary meta-analysis using a complete case analysis followed by sensitivity meta-analyses imputing, in each study, data for those with missing data, and then pooling across studies. For binary outcomes, we suggest use of ''plausible worst case'' in which review authors assume that those with missing data in treatment arms have proportionally higher event rates than those followed successfully. For continuous outcomes, imputed mean values come from other studies within the systematic review and the standard deviation (SD) from the median SDs of the control arms of all studies.

Conclusions: If the results of the primary meta-analysis are robust to the most extreme assumptions viewed as plausible, one does not rate down certainty in the evidence for risk of bias due to missing participant outcome data. If the results prove not

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* Corresponding author. Department of Internal Medicine, Clinical Epidemiology Unit, American University of Beirut Medical Center, P.O. Box: 11-0236, Riad-El-Solh Beirut 1107, 2020 Beirut, Lebanon.

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

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robust to plausible assumptions, one would rate down certainty in the evidence for risk of bias.

Keywords: GRADE; Missing participant data; Risk of bias; Systematic reviews; Trials

1. Introduction

The extent to which risk of bias associated with missing participant outcome data (hereafter, missing data) reduce confidence in results represents a key issue for all systematic reviews [1,2]. Currently, the Cochrane Collaboration Handbook [3] focuses on determining whether individual studies are at low or high risk of bias with respect to missing data. When considering whether to rate down for risk of bias across an entire body of evidence, this approach suffers limitations. Assume, for instance, that one sets a threshold of 10% missing data for high risk of bias, and of six studies in a meta-analysis, three have no missing data and three have 12% missing data. How is one to decide whether, across the entire body of evidence, one should—or should not—rate down for risk of bias due to missing participant data?

Sensitivity meta-analyses based on different assumptions can address these issues, particularly if such analyses consider issues beyond simply the frequency of missing data, such as the event rate in the intervention and control groups, the distribution of missing data in intervention and control groups, and the reasons for missingness. The Cochrane Handbook encourages such analyses but, with respect to missing data, does not provide specific guidance regarding how to proceed.

Three prior publications have filled this gap by presenting approaches for systematic reviews of randomized trials to address missing data for binary [4] and continuous outcomes [5,6]. With some modifications, the GRADE Working Group has endorsed these approaches as GRADE guidance to assess the risk of bias associated with missing data in systematic reviews. In this article, we summarize our modified approaches, providing sufficient detail for their application, and provide several illustrative examples.

We present approaches for three situations: binary outcomes; continuous outcomes in which all studies have used the same instruments; and continuous outcomes in which studies have used different instruments to measure the same construct. In each case, the goal is to make inferences for the entire body of evidence for a particular outcome with respect to risk of bias. Within the GRADE framework, the issue is whether reviewers should rate down certainty in the evidence (quality of evidence, or confidence in evidence) for risk of bias due to missing data.

2. Development of methods

In developing our approaches, we formed a group consisting of clinical epidemiologists, methodologists, and biostatisticians, all with extensive experience in systematic reviews. We conducted a systematic survey of the literature addressing possible approaches to handling missing data when conducting a meta-analysis [7–9]. Iterative discussions among the investigators and testing our approaches in a number of systematic reviews completed the process.

The GRADE Working Group reviewed the approaches at a meeting in Vienna in October 2015, providing feedback that led to modifications from what had been previously published. The Working Group reviewed the resulting modifications, and a draft of this study, at a subsequent meeting in May 2016 and there approved the approaches as GRADE guidance.

3. Scope and definitions

This guide is for meta-analyses of trial-level data and does not address methods for meta-analyses of individual participant data that may be available to investigators. We deal only with missing data and not other elements of risk of bias in a body of evidence (e.g., allocation concealment, blinding) that systematic review authors must address.

We define participant outcome data as ‘‘missing’’ if they are unavailable to the reviewers; that is, unavailable to investigators of the primary studies, or available to the primary study investigators but not included in published reports and not provided after inquiry. A common problem when dealing with missing data is identifying whether a group of participants (e.g., those who withdrew consent or violated the protocol) have missing data or not [10–12]. Another problem is that the trial authors are sometimes not clear about how they dealt with participants missing data in their analysis (e.g., excluded them, or made assumptions) [10–13]. Before applying our approach, we recommend making all possible efforts to obtain unreported but potentially available outcome data from primary study authors, or at least understand how they dealt with missing data.

For conceptual clarity, we distinguish the issue of handling of missing participant outcome data from that of intention to treat (ITT) analysis [14]. The basic principle of ITT involves analyzing participants with available data in the arm to which they were randomized. A methodological survey found a large variation in the definition of ITT: some suggest ITT is only possible with complete follow-up; some demand imputation of missing data for an ITT analysis; and some take our position that ITT should be restricted to how one handles participants with available data, and that dealing with missing data should be treated as a separate issue [7]. Thus, what follows begins with a complete case analysis and deals with missing data as a separate issue best addressed in sensitivity analyses.