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Gaps exist in the current guidance on the use of randomized controlled trial study protocols in systematic reviews

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Abstract

Objectives: The use of trial registry records and randomized controlled trial (RCT) study protocols can assist systematic reviewers in evaluating and, possibly, minimizing publication and selective reporting biases. This study examined current guidance on the use of registry records and RCT study protocols from key systematic review organizations, institutes, and collaborations.

Study Design and Setting: Handbooks, guidelines, and standard documents from key systematic review organizations and the EQUATOR network database were identified. Textual excerpts providing guidance on the use of trial registry records, RCT protocols, and ongoing/unpublished studies were extracted independently by two reviewers and coded into a systematic review framework.

Results: Eleven documents published in English between 2009 and 2016 were included. Guidance for using RCT protocols and trial registry records was provided for 7 of 16 framework categories, and guidance for using unpublished and ongoing studies was available for 8 of 16 categories.

Conclusion: This study identified gaps and ambiguities in language in guidance on the use of RCT protocols and trial registry records. To encourage and assist reviewers to use trial registry records and RCT study protocols in systematic reviews, current guidance should be expanded and clarified.

Keywords: Systematic reviews; Study protocols; Trial registries; Publication bias; Selective reporting of outcomes bias; Randomized controlled trials

1. Introduction

Synthesizing research evidence using systematic and rigorous methods has become a key feature of evidence-based medicine and knowledge translation. Systematic reviews use methods to minimize potential biases posing a threat to the integrity of the findings, such as publication bias and selective reporting of outcomes bias. The present study explores the current best practices for using randomized controlled trial (RCT) study protocols and trial registry records to minimize the abovementioned biases when conducting systematic reviews.

The "tendency for investigators to submit manuscripts and of editors and reviewers to accept them based on the strength and direction of the research findings" is referred to as publication bias [14]. RCTs with negative or null findings are more likely to take longer to publish [13] or to remain unpublished [8]. Fig. 1 illustrates the points at which an RCT can drop out of the publication lifecycle, thereafter remaining unpublished and largely invisible to public view. Even when RCTs are published, some outcomes may remain unreported and the unreported outcomes are more often those that are not statistically significant creating potential for outcome reporting bias [8].

A variety of sources (e.g., contacting the researcher, registry records, and protocols) are available for systematic reviewers to find ongoing or unpublished studies and unreported outcomes. This study focuses specifically on registry records and RCT study protocols. Clinical trial registry records and study protocols document the existence of an RCT, offering mechanisms for detecting unpublished studies, ongoing studies, and all planned outcomes. Study protocols and trial registry records

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What is new?

- Little research has examined the optimal methods and procedures for using RCT study protocols and trial registry records in systematic reviews of interventions, despite their role in evaluating and, possibly minimizing, publication and outcome reporting biases.

What this adds to what was known?

- Analysis of the text from the handbooks, guidelines, and standard documents of key systematic review bodies suggests that advice on the use of RCT study protocols and trial registry records is incomplete and that there is ambiguity in the language used within the documents.

What is the implication and what should change now?

- Guidance to systematic reviewers on the use of both registry records and published protocols within standard documents, guidelines, and handbooks needs to be expanded and clarified to encourage inclusion of trial registry records and RCT study protocols in systematic reviews and to improve assessment of bias in systematic reviews.

differ in publication status, level of methodological detail, and temporality (''living'' vs. static document). Trial registry records are housed in publicly accessible trial registry databases (e.g., ClinicalTrials.gov), contain selective methodological information for ongoing and completed RCTs, and allow researchers to update the record to indicate recruitment status, associated publications, and outcome data. Study protocols are typically published in academic journals, contain a detailed description of the trial methods, and the content is static after publication. The information contained in these documents can be used to assess, and possibly mitigate, the effects of publication and outcome reporting biases.

Clear methodological procedures can assist reviewers in optimally using RCT protocols and trial registry records and possibly encourage their inclusion in systematic reviews. Standard documents, guidelines, and handbooks guide systematic reviewers on current best practices. This study examined and described the state-of-the-art guidance on the use of RCT study protocols and trial registry records for minimizing bias in systematic reviews of the efficacy of interventions.

2. Methods

Our primary sources of information about the procedures for using trial registry records and RCT study protocols in systematic reviews were the handbooks, standard documents, and guidelines documents of the key institutes and collaborations devoted to promotion of and standards for systematic reviews. The systematic review bodies, institutes, and collaborations most relevant to this study were the Cochrane Collaboration (www.cochrane.org/), the Joanna Briggs Institute (http://joannabriggs.org/), the York University Center for Reviews and Dissemination (https://www.york.ac.uk/crd/), the Campbell Collaboration (http://www.campbellcollaboration.org/), and the Institute of Medicine (http://www.iom.edu/ - http://www.iom.edu/). A search of the websites of these organizations was conducted in April 2015 and updated in January 2017 to identify all available handbooks, guidelines, and standard documents. The content had to be, at least in part, pertinent to systematic reviews evaluating the efficacy of interventions. When a website had multiple documents, all relevant handbook, guideline, or standard documents were downloaded. However, if multiple versions or editions of a document were present, only the most recent version or edition was selected. Data from new versions of documents identified by the search update were added to the original analysis. Finally, the EQUATOR network database (http://www.equator-network.org/reporting-guidelines/) was searched for systematic review reporting guidelines.

The data extraction and coding procedures of the ''best fit'' framework approach [3] were adapted to extract and code relevant guidance from identified documents. Instead of extracting data and then evaluating the data for themes, in this approach, an existing framework or model was chosen and the data were extracted and coded into the framework. The framework used in this study was based on the steps to conduct a systematic review described in the Cochrane Handbook (version 5.1.0, http://handbook.cochrane.org/). High-level description of these steps (e.g., ''defining inclusion/exclusion criteria'') provided the framework categories. The Cochrane Handbook was chosen as the basis of the framework because of its' comprehensiveness, relevance to the authors' work as Cochrane reviewers, and formative influence on other systematic review standard documents and handbooks. That said, these are not necessarily the ''gold standard,'' nor do they suit each and every purpose. Four categories were related to the literature search: sources, planning and design, documenting and reporting, and managing references. Three categories were related to the selection phase: defining inclusion/exclusion criteria, making inclusion/exclusion decisions, and alternative inclusion/exclusion criteria for RCT study protocols. Guidance relevant to the reporting flowchart was coded into one category. Two categories related to aspects of collecting data: sources of data, and data extraction forms and extracting data from reports. One category concerned the risk of bias from selective reporting of outcomes. The last five categories were analyzing the data (including meta-analysis), addressing reporting biases, presenting results, interpreting