Contemporary Clinical Trials 45 (2015) 2–7

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Are current standards of reporting quality for clinical trials sufficient in addressing important sources of bias?

Edward J. Mills [a,b,*], Dieter Ayers [a], Roger Chou [c], Kristian Thorlund [a,b]

[a] Redwood Outcomes, Vancouver, Canada
[b] Dept. of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada
[c] Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, Portland, USA

ARTICLE INFO

Article history:
Received 24 April 2015
Received in revised form 10 July 2015
Accepted 27 July 2015
Available online 30 July 2015

Keywords:
Randomized clinical trials
Bias
Quality

ABSTRACT

Determining the quality of a randomized clinical trial (RCT) is necessary for decision-makers to determine the believability and applicability of the trial findings. Issues that are likely to affect the utility of RCT evidence include issues of bias, random error and applicability. In this article we focus primarily on issues of bias and examine the evidence for whether reporting methodological items, including allocation concealment, sequence generation, and blinding of participants can be relied upon as evidence of bias. We present the findings of a systematic review of meta-epidemiological studies and a simulation study demonstrating that commonly examined sources of bias likely play little role in treatment exaggeration. We discuss other issues that may additionally influence trial outcomes including sample size, publication bias, and expertise of trialists. We conclude by discussing strategies to moderate the effect of known biases in assessing overall estimates of treatment effects.

1. Introduction: what is reporting quality?

Assessing whether a clinical trial is believable or not represents an important challenge to clinical decision-makers and health technology assessment (HTA) agencies. Given the large number of randomized trials published every year (some estimates place this at about 20,000 randomized trials per year), there is a clear need for decision-makers to be able to distinguish high quality clinical trials from lower quality or fundamentally flawed clinical trials. There are three key contributing factors that can affect the results of a clinical trial, that we will divide into bias, random error, and applicability of results. Bias represents predicable and avoidable influence of behaviors affecting results. Sources of bias that may affect the believability of a trial may include poor trial planning and conduct, poor or inappropriate analysis, and clearly misleading presentation or interpretation of results [1]. Random error is caused by inherently unpredictable fluctuations, that are more pronounced in small trials and multiple evaluations [1]. Applicability relates to whether the findings of a clinical trial are useful to decision-makers in terms of whether the trial asked an important question, enrolled the right population, and examined outcomes of importance to patients. While issues of applicability are germane to each specific disease or clinical question, bias and random error can be reduced with proper planning. For a decision-maker to interpret the quality of a trial, the reader needs to either have a clear and transparent reporting of what was done at each stage of a trial or otherwise have reasons to believe that a trial was competently completed in the least biased manner possible.

In part to aid in the assessment of bias, advocates within the evidence-based medicine (EBM) movement have supported a call for more complete and transparent reporting of clinical trials according to standardized guidance and sought endorsement followed by enforcement by medical journals to ensure checklists for minimum reporting requirements. In 1996, the Consolidated Standards of Reporting Trials (CONSORT) Statement was first published as a consensus based statement on recommendations for reporting individual randomized clinical trials. The statement has been revised 10 times since then to revisit or include additional items deemed important. Several hundred medical journals now endorse and/or enforce minimum standards for reporting randomized trials and similar guidance now extend to systematic reviews, observational studies, the preparation of abstracts, and subspecialty medical disciplines.

The CONSORT statement is considered an evidence-based guidance document on 25 required items to report. The aim of CONSORT is to establish a standardized tool to make reporting of RCTs more transparent and complete. Many of the reporting items in CONSORT are needed to assess risk of bias in a randomized trial. Several items recommended for reporting are based on previous evidence indicating that they may influence a clinical trial outcome, or based on the expert opinion of participants in the consensus group. Other items may fall into the typical components of a manuscript ranging from the title of the manuscript (where guidance recommends using the word "randomized" in the title [item 1a]) through the introduction, methods, results, discussion,

* Corresponding author at: Redwood Outcomes, 302-1505 West 2nd Ave., Vancouver, BC V6H 3Y4, Canada.
E-mail address: emills@redwoodoutcomes.com (E.J. Mills).

http://dx.doi.org/10.1016/j.cct.2015.07.019
1551-7144/

and tables/figures. As illustrated using the example of the title recommendation, several of the reporting requirements are not necessarily related to risk of bias, but may be recommended because the consensus group considered them to be an issue of high relevance to readers for interpreting and understanding the design of a study. Other examples of issues that are unlikely to bias a trial, but may be desirable, include the requirement for a flow diagram of included participants (item 13a), or a rationale for the trial (item 2a). The majority of other required items are requested based on some evidence that they may influence trial quality, and thus should aid readers in assessing the validity of the trial findings. However, as we explore further in this review, how to deal with low quality evidence as assessed by methodological items and incorporating these assessments in meta-analyses remains insufficient.

2. Why does reporting quality matter?

Items recommended for reporting by the CONSORT statement are largely held as being informed by evidence and have substantial overlap with risk of bias and quality checklists used for scoring or evaluating the quality of RCTs [2]. Early work by Schulz et al. was among the first empirical evidence to demonstrate that reporting methodological items in publications may be associated with biasing trial results [3]. In 1995, Schulz et al. examined the effect of failing to report adequate allocation concealment, exclusions after randomization, and whether trials had used double-blinding among 250 RCTs [3]. They found that studies with inadequate reporting of allocation concealment and inadequate double-blinding significantly increased odds ratios by an average of 30% and 17%, respectively, but no significant associations were found with respect to failing to report adequate sequence generation or post-randomization exclusions [3]. Around the same time, Jadad et al. proposed a scale for evaluating the quality of clinical trials that focused on 3 items: randomized allocation, double-blind design, and description of attrition [4]. These and other studies led to many further evaluations of other specific methodological items and the development of quality assessment instruments consisting of multiple methodological items [2]. As a result of these studies, nearly every tool for assessing the quality of a clinical trial includes questions about allocation concealment, sequence generation, and blinding status [5]. The Cochrane Collaboration (arguably the largest network of individuals assessing the quality of RCTs) requires methodological assessment of RCT quality at the level of individual trial, as well as domain specific assessments [6]. The Cochrane risk of bias tool is an instrument for evaluating the extent to which specific methodological issues may influence estimates of treatment effects, with a particular focus on issues related to internal validity, including (1) selection, (2) performance, and (3) detection bias. Other issues of relevance include attrition, reporting, and other bias. For the sake of this article, we will focus on the three former biases, as these are evaluated independent of the trial results, and focus specifically on allocation concealment, sequence generation, and blinding status. See Table 1.

3. What is the evidence that reporting quality matters?

The empirical evidence on effects of methodological shortcomings on estimates of treatment effects is somewhat inconsistent. We performed a rapid systematic review of available studies that examined how allocation concealment, sequence generation, or blinding methods affected estimates of effect using ratio of ratios as effect measures across meta-epidemiological studies. We searched the major electronic databases and supplemented our searches through the bibliographies of published relevant studies, up to April 10, 2015 [2,7].

Of the studies identified by the systematic search, 14 evaluated risk of bias associated with allocation concealment [3,8–22], 7 evaluated effects of sequence generation [3,8,14–17,19,20], and 10 trials evaluated effects of blinding [8–10,14,17–22]. All studies reported ratio of odds ratios, with the exception of Juni et al. 1999 [13], which reported ratio of relative risk. This was converted to ratio of odds ratio using a method previously outlined by Zhang and Yu 1998 [23]. Ratio of odds ratios (ROR) presents the multiplication factor that assesses the magnitude of bias relative to those studies with adequate allocation concealment, sequent generation and blinding.

Fig. 1 displays the estimated effect on ratio of odds ratios of the specific methodological item on treatment effects. Because these studies have substantial overlap between them in terms of individual included studies, we did not pool them. Despite this overlap, the forest plots display the inconsistency between studies examining the same methodological issues. The most comprehensive study, by Savovic et al. [7,19], compiled data from seven contributing meta-epidemiological studies involving 1973 trials from 234 meta-analyses. The authors found a significant ROR of 0.85, 95% Credible Interval [CrI] 0.75 to 0.95 for allocation concealment, but only for subjective outcomes. However, when

Table 1
Cochrane Collaboration's tool for assessing risk of bias (adapted from Higgins and Altman [50]).

Bias domain	Source of bias	Support for judgment	Review authors judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere