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Unreported formal assessment of unblinding occurred in 4 of 10 randomized clinical trials, unreported loss of blinding in 1 of 10 trials

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Abstract

Objectives: Randomized clinical trials often involve blinding as a methodological procedure to avoid bias. Unfortunately, blinding procedures may be unsuccessful, but the risk of unblinding is rarely reported in trial publications. Our primary aim was to assess the occurrence of unreported assessment of the risk of unblinding in randomized clinical trials and to describe the assessment procedures involved. Our secondary aim was to assess the occurrence of unreported suspected or overt unblinding and the mechanisms of unblinding.

Study Design and Setting: A Web-based questionnaire survey of authors to trial publications which did not report risk of unblinding. Respondents were corresponding authors to a random sample of PubMed indexed articles on blinded randomized clinical trials published in 2010. We initially sampled 300 publications of which 24 reported on risk of unblinding.

Results: Of the 276 contacted trial authors, 129 (47%) responded. Assessment of the risk of unblinding was conducted in 56 trials (43%), often based on a pretrial evaluation involving a group of healthy assessors trying to identify differences between experimental and control interventions. When we included informal assessments of the risk of unblinding, the number of trials assessing the risk of unblinding increased to 75 (58%). Suspected or overt unblinding occurred in 14 trials (11%), mostly based on perceptible differences between experimental and control interventions.

Conclusion: Approximately 4 of 10 trials assessed risk of unblinding without reporting such assessments in the trial publication, and approximately 1 in 10 trials identified cases of overt or suspected unblinding, also without reporting them. Unblinding is not an exceptional event in randomized clinical trials; it occurs regularly but is rarely reported.

Keywords: Randomized clinical trials; Blinding; Masking; Unblinding; Methods; Designs; Reporting

1. Introduction

Blinding is an important methodological principle in randomized clinical trials. Blinding reduces the risk of bias in a trial by masking which intervention is experimental and which is control. The most commonly blinded key trial persons are outcome assessors, patients, and health care providers. The degree of bias induced by inadequate blinding may be considerable [1−7]. For example, nonblinded assessors of subjective outcomes (i.e., involving judgment) exaggerate estimated treatment effects, in the form of odds ratios, by 36% [2].

Several forms of bias are minimized by successfully blinding key trial persons. A potentially preventable bias is patients' attempt to please the investigators by reporting symptoms in line with what they perceived as investigators' expectations (response bias). Selective loss to follow-up (attrition bias) may occur when patients in the control group decide to drop out of trials to seek other treatments. Some patients remain in the trial but still seek alternative interventions (cointervention bias) or switch intervention. Outcome assessors sometimes assess patients in the experimental group favorably (observer bias) if they are aware of the treatment assignment [6].

Although blinding is often intended in trials, blinding procedures sometimes do not succeed as intended [8−12]. In one randomized trial, the majority of patients deduced

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What is new?

Key findings

- Assessment of the risk of unblinding was conducted in 56 of 129 (43%) trials often based on pretrial evaluations.
- Suspected or overt unblinding occurred in 14 of 129 (11%) trials mostly based on perceptible differences between experimental and control interventions.

What this adds to what was known?

- Blinding is an important methodological procedure to prevent bias in randomized clinical trials. The CONSORT 2010 statement encourages authors to report key trial persons who were blinded in randomized clinical trials and if relevant, to describe similarity of interventions.
- This study documented that in 4 of 10 trials, trialists assessed risk of unblinding without reporting such assessments in their trial publications and observed suspected or overt unblinding in 1 of 10 trials also without reporting them.

What is the implication and what should change now?

- Blinding procedures in randomized clinical trials may be unsuccessful. We suggest that trialists should routinely report results from assessed risk of unblinding in randomized clinical trials, and if inadvertent unblinding of key trial persons occurred, it should be clearly stated.
- A future revision of the CONSORT 2010 statement's checklist could recommend reporting assessment of the risk of unblinding.

that they received zinc as an experimental intervention because of its bitter taste [8,9]. Also, herbal preparations will often have a distinct taste [10]. In a trial of the effect of magnetic discs for carpal tunnel syndrome, 30% of patients discovered the magnetic property of the experimental intervention [12]. Also, in trials where only the outcome assessor is blinded, nonblinded patients may inadvertently reveal their allocated intervention to the outcome assessor. For example, in a trial of cognitive behavioral therapy for major depressive disorder, 64 of 334 patients (19%) disclosed their allocation status to the outcome assessor [13].

The risk of compromised blinding, or "unblinding," is of major importance when interpreting the validity of a trial result, either informally or as part of a formal assessment of risk of bias, for example, when a trial is included in a systematic review. However, reliable assessment of the risk of bias due to insufficient blinding is often thwarted by inadequate reporting in trial publications [14–16]. More than 90% of publications of blinded randomized trials do not report on the risk of unblinding [16]. This may reflect that no unblinding was observed, a lack of tradition for reporting the issue, lack of methodological guidelines as how best to assess unblinding, or simply that unblinding was not considered important. Regardless, it is unfortunate that risk of unblinding in blinded trials is most often unknown for readers of most publications of randomized trials, for researchers conducting systematic reviews of randomized trials, and for the users of such reviews.

Thus, we conducted a survey among authors of trial publications that did not report on risk of unblinding. Our primary aim was to assess the occurrence of unreported assessment of the risk of unblinding in randomized clinical trials and to describe the assessment procedures involved. Our secondary aim was to assess the occurrence of unreported suspected or overt unblinding and the mechanisms of unblinding.

2. Methods

The study was a Web-based questionnaire survey.

2.1. Trial inclusion criteria

We sampled 300 randomly selected publications indexed in PubMed in 2010 (PubMed date limit 01.01.2010–31.12.2010) and describing blinded randomized clinical trials. In a previous study, we reviewed the 24 of the 300 publications that reported on risk of unblinding [16]. In this study, we included the remaining 276 trial publications that did not report on the risk of unblinding.

2.2. Survey procedure

We e-mailed the corresponding authors of the 276 trials between 21 November, 2013 and 11 February, 2014. The authors were asked to link on to a Web-based questionnaire on issues related to blinding in their trial. We informed the authors of the aims of the survey and assured them of strict confidentiality and that only aggregate data would be published. Reminders were sent to trial authors after 2 weeks and thereafter weekly until questionnaire responses stopped.

2.3. Survey instrument

We developed a 24-item questionnaire with both open- and close-ended questions. The questionnaire was pretested twice on corresponding authors to trials not included in the main survey, and modifications were made accordingly.

Questionnaire items were grouped into four sections (Appendix at www.jclinepi.com). Section I covered basic trial information, for example, trial type and key trial persons intended to be blinded. Section II covered information