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REVIEW ARTICLES

The risk of unblinding was infrequently and incompletely reported in 300 randomized clinical trial publications

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Abstract

Objectives: To assess the proportion of clinical trials explicitly reporting the risk of unblinding, to evaluate the completeness of reporting on unblinding risk, and to describe the reported procedures involved in assessing unblinding.

Study Design and Setting: We sampled at random 300 blinded randomized clinical trials indexed in PubMed in 2010. Two authors read the trial publications and extracted data independently.

Results: Twenty-four trial publications, or 8% (95% confidence interval [CI], 5, 12%), explicitly reported the risk of unblinding, of which 16 publications, or 5% (95% CI, 3, 8%), reported compromised blinding; and 8 publications, or 3% (95% CI, 1, 5%), intact blinding. The reporting on risk of unblinding in the 24 trial publications was generally incomplete. The median proportion of assessments per trial affected by unblinding was 3% (range 1−30%). The most common mechanism for unblinding was perceptible physical properties of the treatments, for example, a difference in the taste and odor of a typhoid vaccine compared with its placebo.

Conclusion: Published articles on randomized clinical trials infrequently reported risk of unblinding. This may reflect a tendency for avoiding reporting actual or suspected unblinding or a genuine low risk of unblinding.

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

1. Introduction

Blinding is an important methodological procedure in randomized clinical trials. In most trials, the aim of blinding is to avoid bias by keeping key trial persons, such as patients, health care providers, or outcome assessors, unaware of allocated treatment [1−3].

Successful blinding of patients and treatment providers has the potential to prevent various forms of bias due to a systematic difference between control and experimental groups. Blinding minimizes cointervention bias (ie, bias due to the differential use of cointerventions), attrition bias (ie, bias due to differential patient dropout), or response bias (ie, bias due to differential reporting of symptoms) [3]. Blinding also ensures a similar degree of placebo effects in the compared groups [3]. Successful blinding of outcome assessors protects against observer bias, also called ‘‘detection bias’’ or ‘‘ascertainment bias’’ [3]. Metaepidemiologic studies report that trials that are not double blind exaggerate treatment effects (odds ratios) by 13%, and by 23% when outcomes are subjective [4]. Similarly, studies of trials with both blinded and nonblinded assessors of subjective outcomes found that lack of blinding exaggerated treatment effects considerably; for example odds ratios by ~36% [5−7].

Methods to blind key trial persons vary considerably and range from the simple designs, such as withholding treatment identity information, to complex designs, such as simulation of surgical procedures [8,9]. Randomized clinical trials of nonpharmacological treatments may be more difficult to blind [9,10], partly because of the challenge of developing inert control intervention that appears identical to the active treatment [10].

Blinding procedures may not be effective, and loss of blinding, that is, unblinding, occurs in an unknown proportion of trials. Compromised blinding has generated some concern [3,11−16], especially within psychiatry [15] and oncology [16]. Experimental interventions in trials may have tell-tale characteristics (eg, taste or aftertaste, smell, or side effects) that make blinding difficult to establish and maintain. Eby et al. [17], compared the efficacy of zinc gluconate with calcium lactate placebo in a blinded

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What is new?

Key findings

- Of 300 blinded randomized clinical trial publications, 8% (95% confidence interval [CI], 5, 12%) reported the risk of unblinding, of which 5% (95% CI, 3, 8%) reported that blinding had been compromised and 3% (95% CI, 1, 5%) that blinding was intact.
- The most commonly implicated mechanism for unblinding was perceptible physical properties of treatments.
- The median proportion of assessments affected by unblinding was 3%, but varied considerably.

What this study adds to what was known?

- Lack of blinding in randomized clinical trials is an important source of bias. Risk of unblinding of key trial persons is infrequently reported in trial publications.
- When the risk of unblinding is addressed in trial publications, reporting tends to be incomplete.

What is the implication and what should change now?

- We suggest that trial publications should routinely report procedures intended to prevent, record, and deal with cases of overt unblinding or the absence of such procedures.
- Further methodological research is needed to develop procedures to assess the risk of unblinding.

common cold trial and found that about half of the patients in the zinc gluconate group reported problems with taste due to the distinctive metallic aftertaste of zinc [14,18]. DuBeau et al., in a trial of an antimuscarinic drug, reported that patients who had the side effect, dry mouth, correctly identified that they were randomized to the active intervention [12].

Unblinding may be obvious in some cases, but in other cases, trialists may only have a suspicion that blinding procedures were not fully effective. Unfortunately, there is a lack of methodological consensus on how to best assess the risk of unblinding. Testing for the success of blinding is sometimes done by asking key trial persons to guess treatment allocation [13,19] with the assumption that a high proportion of correct guesses would imply partially unsuccessful blinding. However, a guess may often be linked to hunches about efficacy of treatments [20–22], so the interpretation of the test is challenging [13,19]. Such tests are rarely implemented [19]. Some trialists may assume intact blinding unless overt cases of unblinding occur. Ideally, this approach requires careful considerations of the procedures in place for assessing unblinding, including explicit thresholds for when blinding is considered compromised. We are unaware that any such standard procedures or operational thresholds have been published, and this aspect of planning and running a trial remains a challenge.

Thus, we were interested in how authors of randomized clinical trial publications reported the risk of unblinding. Our primary aim was to assess the proportion of trial publications explicitly reporting on the risk of unblinding. Our secondary aims were to evaluate the completeness of reporting on the risk of unblinding and to describe the procedures involved in assessing unblinding.

2. Methods

We randomly sampled and read 300 publications describing blinded randomized clinical trials indexed in PubMed in 2010.

2.1. Search strategy

We developed a database of randomized clinical trials indexed in PubMed and published in 2010. We used a modified Cochrane highly sensitive search strategy for identifying randomized clinical trials indexed in PubMed [23], adding a date limit for the most recently completed year before study onset (January 1, 2010–December 31, 2010) and the search term ‘‘(blind* OR mask*)’’. We identified 9,937 references.

2.2. Eligibility criteria

We included blinded randomized clinical trial publications published in English and indexed in PubMed in 2010. We excluded secondary trial reports, nonblinded and nonrandomized trials, observational studies, and reviews (see Supplementary Fig. 1 at www.jclinepi.com).

We arbitrarily aimed to identify 25 trial publications that reported the risk of unblinding. We defined *unblinding* as any loss of blinding that was not envisaged by the trial protocol; this excludes emergency unblinding to enhance better management of patients in case of serious adverse events, except when this led to further unintended loss of blinding. We defined reporting the risk of unblinding in trial publications as (1) explicit description of compromised blinding or a suspicion of compromised blinding, that is, high risk of unblinding (eg, overt events or structural deficiencies in the trial or authors’ perception from interpretation of any test of blinding, suggesting unblinding) or (2) explicit description of intact blinding, that is, low risk of unblinding (eg, a description of no observed cases of unblinding or authors’ conclusion of no unblinding based on interpretation of test of blinding).