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ORIGINAL ARTICLE

Cohort study of trials submitted to ethics committee identified discrepant reporting of outcomes in publications

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Abstract

Objectives: To identify factors associated with discrepant outcome reporting in randomized drug trials.

Study Design and Setting: Cohort study of protocols submitted to a Swiss ethics committee 1988−1998: 227 protocols and amendments were compared with 333 matching articles published during 1990−2008. Discrepant reporting was defined as addition, omission, or reclassification of outcomes.

Results: Overall, 870 of 2,966 unique outcomes were reported discrepantly (29.3%). Among protocol-defined primary outcomes, 6.9% were not reported (19 of 274), whereas 10.4% of reported outcomes (30 of 288) were not defined in the protocol. Corresponding percentages for secondary outcomes were 19.0% (284 of 1,495) and 14.1% (334 of 2,375). Discrepant reporting was more likely if P values were <0.05 compared with $P \geq 0.05$ [adjusted odds ratio (aOR): 1.38; 95% confidence interval (CI): 1.07, 1.78], more likely for efficacy compared with harm outcomes (aOR: 2.99; 95% CI: 2.08, 4.30) and more likely for composite than for single outcomes (aOR: 1.48; 95% CI: 1.00, 2.20). Cardiology (aOR: 2.34; 95% CI: 1.44, 3.79) and infectious diseases (aOR: 1.77; 95% CI: 1.01, 3.13) had more discrepancies compared with all specialties combined.

Conclusion: Discrepant reporting was associated with statistical significance of results, type of outcome, and specialty area. Trial protocols should be made freely available, and the publications should describe and justify any changes made to protocol-defined outcomes.

Keywords: Randomized controlled trial; Ethics committee; Drug industry; Treatment outcome; Publication bias; Statistics and numerical data

1. Introduction

Publication bias, the selective publication of randomized trials and other studies depending on their results, is a well-documented threat to evidence-based practice: if the data that are accessible to clinicians and policy makers are distorted toward positive results, treatment recommendations may turn out to be inappropriate [1−4]. There is selective reporting of not only entire studies with ‘‘positive’’ results but also some outcomes but not others, depending on the nature and direction of the results [5,6]. The conclusive documentation of such ‘‘outcome reporting bias’’ requires access to the study protocols, and any protocol amendments to determine whether and how an outcome was defined at the protocol stage. The reporting of outcomes in the subsequent journal publications can then be compared with the protocols, and outcomes that were omitted, changed, or added can be identified.

A first pilot study comparing 15 trial protocols with matching journal articles was published in 2002 [7]. Chan et al. [8,9], in two larger studies, examined 102 protocols of trials submitted to two Danish research ethics committees and 48 trials approved for funding by the Canadian Institutes of Health Research protocols. They found that statistically significant outcomes were more likely to be

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Ethical approval: This study was approved by the Ethics Committee and the legal division of the Department of Health of the Canton of Bern.

Competing interests: The authors have declared that no competing interests exist.

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What is new?

Key findings

- We compared protocols of drug trials with matching journal publications. Discrepant reporting of outcomes was defined as the addition, omission, or reclassification of primary and secondary outcomes.
- Discrepant reporting was more likely for efficacy compared with harm outcomes and more likely for composite compared with single outcomes.
- Cardiology and infectious diseases had more discrepancies compared with the average of all clinical specialties.

What this adds to what was known?

- This is the largest cohort of drug trials so far, and one of few studies that examined both primary and secondary outcomes.
- Discrepant reporting of outcomes was associated with not only statistical significance of results but also the type of outcome and the specialty area.

What is the implication and what should change now?

- Trial protocols should be made freely available, and the publications should describe and justify any changes made to protocol-defined outcomes.

fully reported in subsequent publications than nonsignificant outcomes. More recently, Mathieu et al. [10] compared the primary outcomes specified in trial registries with those reported in the published articles. Among 147 trials registered before study end with a clear description of the primary outcome, 31% (46 of 147) showed some discrepancies between registered and published primary outcomes. A recent Cochrane methodology review identified six studies comparing the reporting of outcomes in study protocols to published reports and three comparing trial registry entries to published reports [6]. Most of the previous studies of outcome reporting examined primary outcomes only, rather than all outcomes defined in the study protocol [6], and two studies [8,9] focused on the reporting of sufficient data to allow inclusion of the study into a meta-analysis. With the exception of the association between reporting of an outcome and its statistical significance ($P < 0.05$), the determinants of concordant or discrepant reporting in journal publications of primary and secondary outcomes defined in the study protocol are not well defined at present. In particular, previous studies found no consistent associations with funding source or size of trials [6].

We aimed to identify factors associated with discrepant reporting of primary and secondary outcomes including the addition, omission, or reclassification of primary and secondary outcomes in a large cohort of protocols of randomized drug trials submitted over 11 years to the ethics committee of a Swiss University hospital.

2. Methods

2.1. University Hospital Bern cohort of study protocols

The cohort of study protocols submitted from 1988 to 1998 to the Research Ethics Committee of the University Hospital Bern (Inselspital), Switzerland, and the factors affecting publication or nonpublication of results have been described previously [11]. Briefly, the submissions consisted of study protocols and cover letters and, in some instances, amendments submitted later on. Detailed statistical analysis plans were generally not part of the submissions, and there were no standardized submission forms. We included all randomized trials of drug interventions in patients and identified corresponding publications in electronic searches and a survey of authors. We excluded drug trials in healthy volunteers. We searched the CENTRAL database (Cochrane Library, issue 02/2006), which includes trials published in journals indexed and not indexed in MEDLINE, Embase, or other bibliographic databases and trials published in languages other than English [12]. From April to July 2006, we sent standardized questionnaires to the investigators of all included protocols, asking investigators to confirm that the publications corresponded to the study protocol and that the list of publications was complete [11]. We also searched the MEDLINE (PubMed) database to identify more recent publications. The last searches were done in February 2009. We developed a search strategy for each protocol, based on information such as the study name or acronym, condition studied, and the names of the applicants. This study was approved by the Ethics Committee and the legal division of the Department of Health of the Canton of Bern.

2.2. Data collection and definitions

A standardized form was used to extract data on study characteristics, sample size, source of funding, and prespecified outcomes from all eligible protocols. The outcomes were classified as primary outcomes if they were specified as such or used in a sample size calculation; otherwise they were classified as secondary outcomes. We defined an efficacy outcome as an outcome that should be prevented or improved by administering the study drug, and a harm outcome as side effects or adverse events of the study drug. If several adverse events were prespecified, then they were treated as separate outcomes. Outcomes were further classified as binary, continuous (including discrete data), and time-to-event outcomes and whether they were composite