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Comparison of noninferiority margins reported in protocols and publications showed incomplete and inconsistent reporting

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Abstract

Objectives: To compare noninferiority margins defined in study protocols and trial registry records with margins reported in subsequent publications.

Study Design and Setting: Comparison of protocols of noninferiority trials submitted 2001 to 2005 to ethics committees in Switzerland and The Netherlands with corresponding publications and registry records. We searched MEDLINE via PubMed, the Cochrane Controlled Trials Register (Cochrane Library issue 01/2012), and Google Scholar in September 2013 to identify published reports, and the International Clinical Trials Registry Platform of the World Health Organization in March 2013 to identify registry records. Two readers recorded the noninferiority margin and other data using a standardized data-abstraction form.

Results: The margin was identical in study protocol and publication in 43 (80%) of 54 pairs of study protocols and articles. In the remaining pairs, reporting was inconsistent (five pairs, 9%), or the noninferiority margin was either not reported in the publication (five pairs, 9%) or not defined in the study protocol (one pair). The confidence interval or the exact *P*-value required to judge whether the result was compatible with noninferior, inferior, or superior efficacy was reported in 43 (80%) publications. Complete and consistent reporting of both noninferiority margin and confidence interval (or exact *P*-value) was present in 39 (72%) protocol-publication pairs. Twenty-nine trials (54%) were registered in trial registries, but only one registry record included the noninferiority margin.

Conclusion: The reporting of noninferiority margins was incomplete and inconsistent with study protocols in a substantial proportion of published trials, and margins were rarely reported in trial registries.

Keywords: Noninferiority trials; Noninferiority margin; Study protocols; Journal publications; Trial registration; Completeness of reporting

1. Introduction

A noninferiority trial (NIT) measures a new treatment against a standard treatment to determine if it is not substantially worse. NITs are useful when benefits of standard therapy are known, and when novel treatments may be easier to use, less costly, or have fewer side effects [1]. NITs also can test pharmacologically related compounds to see if they are similarly effective [2]. A new treatment is considered noninferior if the trial demonstrates that the new treatment is unlikely to be worse than an established treatment by more than a prespecified amount, the *noninferiority margin*. A noninferiority margin that is too wide may compromise the results, and encourage acceptance and use of less-effective therapies [3,4]. The number of published noninferiority studies has substantially increased in recent years [5].

The interpretation of results of NITs is challenging [4]. It requires an assessment of the rationale for the design and the assumptions underlying the choice of the noninferiority margin [6]. Because readers generally have no access to study protocols, the complete and accurate reporting of what was planned is essential [7]. Guidelines for the design

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What is new?

Key findings

- Discrepancies between protocols and publications of randomized clinical trials are well documented. We compared protocols of noninferiority trials submitted to ethics committees with matching journal publications and examined records in trial registries.
- Concordant reporting of margins and adequate reporting of confidence intervals or exact *P*-values (required to judge whether the result was compatible with noninferior efficacy) was present in approximately 70% of publications.

What this adds to what was known?

- This is the first study of protocols of noninferiority trials and matching journal publications. The reporting of noninferiority margins was incomplete and inconsistent with study protocols in a substantial proportion of published trials, and margins are rarely reported in trial registries.

What is the implication and what should change now?

- Trial registries should facilitate the recording of the noninferiority design and margin. Future revisions of reporting guidelines should ask authors to detail and justify changes to noninferiority margins. Most importantly, trial protocols should be made freely available.

and conduct of NITs have been issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [8,9] and by the Committee for Medicinal Products for Human Use [10]. The Consolidated Standards of Reporting Trials (CONSORT) statement has been extended to improve the reporting of such trials [7]. The integrity of the NIT cannot be affirmed if authors do not accurately report the prespecified noninferiority margins and the relevant confidence intervals [11]. Authors must document the margins selected during the planning phase, and ensure that these margins are not chosen or modified post hoc, during analysis [4].

Some investigators modify design elements of a study, driven by their results. The post hoc modification of outcomes in randomized trials is a well-documented practice [12,13]. For example, a recent study of almost 3,000 outcomes of (superiority) trials submitted to an ethics committee in Switzerland showed that in 30% of studies there were discrepancies between definitions in the protocols and in publications [14]. The risk of incorrect reporting is potentially greater for NITs than for superiority trials. In superiority trials, the tested hypothesis is always the null hypothesis of no difference, which cannot be altered a posteriori. If the confidence interval on the difference includes 0, the new treatment is considered to be no better than the reference treatment. In contrast, an NIT tests the hypothesis that the new treatment is less effective than the reference treatment by an acceptable amount, captured by the noninferiority margin. Because the choice of the margin is to some extent arbitrary, researchers may be tempted to redefine the margin once the results are in, to claim noninferiority. At present, it is unknown whether this happens or not.

Our goal was to compare protocols of NITs submitted to ethics committees with published articles reporting the results of these NITs. We assessed the noninferiority margins reported in protocols and publications, with the intent of determining whether the margins were concordant between protocols and publications. We also identified the studies that had been registered in a publicly accessible trial registry and examined whether or not the noninferiority design and margin had been included in the registry record.

2. Methods

2.1. Identification of protocols of noninferiority trials

In July 2012 we searched for protocols of NITs in databases and archives of three research ethics committees: Kantonale Ethikkommission Bern (the Canton of Bern, Switzerland, see www.kek-bern.ch); Commission d'éthique de la recherche sur l'être humain (the Ethics Commission of University Hospitals of Geneva, Switzerland, see www.hug-ge.ch/ethique); and Ethische Commissie Leids Universitair Medisch Centrum (the ethics committee of Leiden University Medical Center in the Netherlands, www.lumc.nl). We restricted our search to protocols submitted between January 1, 2001, and December 31, 2005. The noninferiority design is relatively new, and few noninferiority studies were published before 2001 [15]. We chose a cutoff date at the end of 2005 to allow enough time for the studies to be conducted and published.

A study protocol was eligible for inclusion if it described a NIT or equivalence trial or stated that its goal was to determine whether a treatment was no worse than its comparator. When reviewing protocols for eligibility, we paid particular attention to the summary description of the study, the hypothesis that was tested, the statistical methods, and the determination of sample size. We included all NITs, without regard to the number of arms, the intervention examined, or the inclusion of a noninferiority margin in the protocol.

2.2. Identification of matching publications

In September 2012, we systematically searched for subsequent publications of each included study protocol in PubMed (National Library of Medicine), the Cochrane