



Efficacy of experimental treatments compared with standard treatments in non-inferiority trials: A meta-analysis of randomized controlled trials.

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**Efficacy of experimental treatments compared with
standard treatments in non-inferiority trials: A meta-
analysis of randomized controlled trials.**

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IJE-2009-10-0935 Efficacy of experimental treatments compared with standard treatments in non-inferiority trials: A meta-analysis of randomized controlled trials.

Referee comments in black, authors' response in blue, changes in red and italic.

General response to the referees' comments:

We think that we may not have explained our hypothesis and the focus of our study well enough. The question that we address in this study is whether a verdict of 'proven' non-inferiority for experimental treatment somehow hides a consistently lesser effect than standard treatment. We have revised the introduction as follows, to emphasize the focus of our paper:

There is concern that non-inferiority trials might be deliberately designed to conceal that a new treatment is somewhat less effective than a standard treatment.^{10,12} Systematic use of too large non-inferiority margins or systematic biases of design, conduct or reporting of non-inferiority trials may skew results in favour of new treatments.¹⁴⁻¹⁹ In this meta-analysis we examined one type of systematic bias. If trialists systematically compare slightly less effective new treatments to standard treatments, the combined results from a meta-analysis of many trials in which experimental treatments gain a verdict of non-inferiority, would be expected to favour the standard treatment. To test this hypothesis we performed a meta-analysis of non-inferiority trials published in clinical journals and assessed the average effect of experimental treatments compared with standard treatments. Importantly, the combined estimate from the meta-analysis will not be influenced by the choice of the non-inferiority margins.

Referee: 1

Comments to the Author

To the Author.

This paper represents a considerable effort in establishing the value of non-inferiority trials.

The paper is well written, concise and quite critical in establishing strengths and weaknesses of the study. However to recognize the limitations is not a reason to allow a conclusion. The strong message derived from this paper is in fact not reliable because, as the AA report them selves, the recognition of bias does not rule out that the experimental treatments are inferior to the standard interventions. The study is based on 30 percent of the non inferiority trials only. There has been no attempts to find unpublished trials. No evaluation has been made on the quality of the recruited trials.

There are two points that should be included in the paper

1. a critical analysis of the delta utilized

We acknowledge that this is an important issue, but please note that the focus of our paper is on the combined results from the meta-analysis. The combined estimate from the meta-analysis will not be influenced by the choice of the non-inferiority margins. An assessment of the appropriateness of non-inferiority margins in relation to the outcome examined was outside the scope of this study. This would have required an in-depth analysis of each trial with subject matter

knowledge on each topic. We have revised the introduction to emphasize the focus of our paper. Please see our 'general response to the referees' comments'.

2. an analysis of the standard therapy; it should be established if the standard represents the best available therapy. It is in fact obvious that if poor standards are selected everything may become non inferior.

The reviewer is right in pointing out that this is an important issue in non-inferiority and in superiority trials in which an active comparator treatment is used, but please note that the focus of our paper is on the combined results from the meta-analysis. An assessment of the appropriateness and efficaciousness of the standard treatments would have required an in-depth analysis of each trial with subject matter knowledge on each topic. This was outside the scope of this study. As suggested by the reviewer we have added an analysis to assess how standard treatments performed in view of the expected efficacy as stated by trialists.

Methods:

We compared the observed incidence of the primary endpoint in the group that received standard treatment with the expected incidence, as specified by the trialists. The result was expressed as a ratio. If needed, the inverse of this ratio was calculated, so that ratios below 1 consistently indicated that the standard treatment performed better than was expected at the design stage of the trial, and ratios above 1 indicated that the standard treatment performed worse than was expected. This ratio could not be calculated for studies that did not report separately the expected, or the observed incidence of the primary endpoint, or studies reporting continuous endpoints.

Results:

The ratio of the observed and expected incidence of the primary endpoint in the group that received standard treatment could be calculated for 112 comparisons. Fifty-three percent of comparisons (n=59) had a ratio below 1, indicating that the standard treatment performed better than was expected at the design stage of the trial and 46% (n=51) above 1, indicating that the standard treatment performed worse than was expected. Two ratios were exactly 1. The mean ratio was 0.941 (95% CI 0.859 to 1.030), meaning that on average the chosen standard treatments performed slightly better than was estimated at the design stage of the trials. Stratified by source of funding, this ratio was 0.974 (95% CI 0.865 – 1.097) for 55 studies funded by industry and 0.906 (95% CI 0.760 to 1.080) for 31 studies funded by public sources. These two estimates did not differ significantly (p=0.5 from t-test for equality of means).

Discussion:

The combined estimate will be influenced by the efficaciousness of standard treatment. If the standard treatment is not effective, the experimental treatment is in fact tested against 'placebo' in a non-inferiority design. Although we did not assess whether the chosen standard treatment represented the best available comparator, we did assess how standard treatments performed in view of what

trialists had expected. On average the standard treatments performed slightly better than was estimated at the design stage of the trials.

Furthermore efficacy is only one part of the problem; the possibility that a treatment could be no less effective but more toxic should be excluded before any conclusion is reached.

We agree. There is a trade-off between efficacy and toxicity. In our meta-analysis, six studies deemed the experimental treatment to be clinically inferior based on a secondary 'toxicity end-point'. Systematic assessment of toxicity in a meta-analysis would require that we judge the trade-off between the benefit and the drawback for each individual experimental treatment and come to a combined endpoint. Such an analysis would be quite subjective and was beyond the scope of our study. We have added a paragraph in the discussion addressing the issue of toxicity. p13:

Of the 175 comparisons in this meta-analysis, we considered the experimental treatment to be non-inferior in 130 (74%) and superior in 15 (9%). Although in 6 of these 145 comparisons the authors deemed the experimental treatment to be clinically inferior based on a secondary end-point, the majority of published non-inferiority trials can be used to support the registration of a new treatment. The added value and safety of these treatments may not always be self-evident and may not always be demonstrated in the trial. The follow-up time and the sample size of trials is limited, making it improbable that rarer side effects or long term side effects are detected.

From a statistical standpoint, analysis has been conducted according to standard methodology. However, the relevance of the primary analysis is questionable, since a result close to unity should be expected, while focus on differences in precision of the estimates might be of more interest.

We think that we may not have explained our hypothesis and the focus of our study well enough. The question that we address in this study is whether a verdict of 'proven' non-inferiority for experimental treatment somehow hides a consistently lesser effect than standard treatment. We have revised the introduction as follows, to emphasize the focus of our paper: See our 'general response to the referees' comments'.

Besides a critical analysis of delta utilized, the evaluation of the differences between observed and hypothesized point estimates would be welcome too.

See our response to point 1 and 2.

Referee: 2

Comments to the Author

General comments

The papers aims at providing evidence on the current debate about the pros and cons of non inferiority trials which, in Authors words: “ can be deliberately designed to conceal that a new treatment is less effective than a standard one”

To do this Authors performed a metanalysis of all non inferiority RCTs published between 1991 and February 2009 searching the 115 journals included into PubMed selection of core clinical journals.

Authors found that the average relative risks comparing experimental with standard treatment was close to 1 thus concluding that non inferiority trials are not systematically less effective than standard treatments. Authors acknowledge that their study has several important limitations, and that further studies are warranted before a firm conclusions about the benefit risk profile of this sort of trials can be reached.

Overall, this reviewer has reservations about:

- the process through which Authors reached their conclusion - see point 2) below;
- the presentation of the results - see point 1) and 3) below
- the failure to analyze in greater depth some of their results – see point 4 below.

Specific Comments

1. Abstract

The abstract is unbalanced, and somewhat falsely reassuring. It in fact emphasizes that “....non inferiority trials published in core clinical journals are not systematically less effective than the standard treatment”. The thorough examination of the limitations of the review, which is in the discussion, does not allow to come safely to this conclusion.

We have modified the conclusion of the abstract as follows:

In this meta-analysis of non-inferiority trials the average relative risk comparing experimental with standard treatments was close to 1. The experimental treatments that gain a verdict of non-inferiority in published trials do not appear to be systematically less effective than the standard treatments. Importantly, publication bias and bias in the design and reporting of the studies cannot be ruled out and may have skewed the study results in favour of the experimental treatments. Further studies are required to examine the importance of such bias.

2. Methods

Besides the limitations of their search strategy that the Authors discuss on page 11 (Discussion section lines 19-39), it should be noted that there are also other reasons why the search strategy can be challenged as of its ability to identify all relevant studies. Authors in fact do not discuss the consequences of their choice to base their search on the 3 main key words “noninferiority”, “noninferiority”, “equivalence”. It is, I believe, possible that poorer quality studies are also those poorly indexed, and this potential loss would disproportionately affect studies with more methodological problems. Specifically, a “negative study” (i.e a study that found no statistically significant difference between new and standard treatments) may not be labelled as “non inferiority” and be used in practice to claim demonstration of “non inferiority study”. I recognize that this is an

issue that does not have an easy solution but given that cannot be ruled out should have inspired greater caution to the Authors.

Obviously, this would have required a completely different sampling strategy (ie. full identification of all studies conducted in a specific disease/condition and then classification - according to the directions and statistical significance of the results).

It would at least be legitimate to mention this issue in the discussion at least to hypothesize what would have happened to this metaanalysis had these studies been systematically searched and included?.

Thank you for this comment. To pick up your challenge we did a quick full text search of a limited number of journals that were included in our meta-analysis. We did indeed find a number of additional non-inferiority trials that were not mentioned as such in title or abstract. Interestingly, just under half of these 'missed trials' were designed as two-step trials, meaning that the methods section stated that a test for superiority would be performed in case of a verdict of non-inferiority. In two thirds of these trials the point estimate favoured experimental treatment and in half of the trials the authors' deemed experimental treatment to be statistically superior. This 'quick and dirty' sensitivity analysis suggests that if anything, adding the trials found in full text would have skewed the results of our meta-analysis in favour of experimental treatment. This would not invalidate or change our main conclusion which focussed on the question whether a verdict of 'proven' non-inferiority somehow hides a consistently lesser effect than standard treatment. Thank you for pointing this out. The trials with a 'two-step analysis' that are the cause of this finding (they are the ones that lead to the favouring of the experimental treatment) may become the focus of our next effort, as they seem special! However, they were not the focus of this report. In the discussion we address this issue as follows (p11):

Our study has several strengths and limitations. We aimed to include all the non-inferiority trials published in these journals, irrespective of the type of endpoints or measures of effect. We restricted the search to the group of core clinical journals, as defined in PubMed, which is the same group of journals as in the Abridged Index Medicus (AIM). This selection covers a wide range of journals from many clinical specialties. Our results may therefore be representative for non-inferiority trials published in other journals. However, external validity may be limited to higher quality journals. If non AIM journals are of lower quality, the characteristics of non-inferiority trials published in those journals might be different. Furthermore, our search would have missed trials that do not mention the non-inferiority design in the abstract, the title or as a key word. The characteristics of such trials might also differ.

3. Results section page 8 and 9.

This metaanalysis somewhat refers to a non real situation. "Non inferiority trials" - if used for registration purposes - are, in real life, presented to regulatory bodies in isolation (at most an handful of them). In my view it does not make much sense to look at their overall significance and direction without taking this into account. At the bottom of page 8 Authors state that: ".....in 74% comparisons experimental treatment was non inferior". This means that, in most cases, these trials can be used to support the registration of a

new intervention no matter how good they were designed. Authors acknowledge this on page 12 but then they do not draw the consequences of it. If one wants address and discuss what happens in reality, namely the way drugs are licensed this can (and should) be the main finding of the study. To me that result is much more important than saying that "...of the 130 comparisons judged to be non-inferior 58% favoured the experimental treatment and 42% the standard ..." (see page 8 line 45-8). The latter looks to me an elegant statistical results but of very limited (and as said, somewhat misleading) practical significance.

We agree that it is important for readers to realize that the majority of published non-inferiority trials can be used to support the registration of a new intervention. However, this was not the main focus of this meta-analysis (see our 'general response to the referees' comments'). In the discussion we now do draw the conclusion from the fact that ".....in 74% comparisons experimental treatment was non inferior " (p13).

Of the 175 comparisons in this meta-analysis, we considered the experimental treatment to be non-inferior in 130 (74%) and superior in 15 (9%). Although in 6 of these 145 comparisons the authors deemed the experimental treatment to be clinically inferior based on a secondary end-point, the majority of published non-inferiority trials can be used to support the registration of a new treatment.

4. Influence of source of funding

This should have been explored more thoroughly. On page 9 (lines 43-49) Authors state that "the main results and the results from the stratifies analysis where similar with the two statistical model were similar except for a difference in those stratified by funding sources". Readers would legitimately like to know more on that as one of the main concern about the (mis)use of inferiority trials is exactly the possible inappropriate use in commercially sponsored studies. Findings reported in table 2 should, in other words be better discusses as the category of industry funded trials is the one whose upper 95% CI is 1.00) Thus more information should be provided and discussed.

We now discuss this finding on p13:

The finding that studies sponsored by industry were more likely to have results favouring sponsored treatments is in line with other reports.^{15,25 26} Systematic bias has been suggested as a possible explanation. Our finding could also be due to the play of chance.

5. Representativeness of the sample

Authors state in the discussion section that their sample is representative (page 11 lines 24-39). This reviewer is surprised by the distribution of the "fields" of the "non inferiority trials" shown in Table 1. In particular the proportion of oncology trials seem disproportionately low and the fact that 1 out of 5 come from a lumped category "others" is rather uninformative.

The Abridged Index Medicus does not include some important journals on oncology such as the Journal of Clinical Oncology and journal of the national

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cancer institute. Furthermore, in a systematic review of 327 publications Lange and Freitag found only a slightly larger proportion of oncology trial (8.7%) (Lange S, Freitag G. Choice of delta: requirements and reality--results of a systematic review. *Biom J* 2005;47:12-27). The most common 'fields in medicine' in the category 'other' were: general medicine (3%), pulmonary medicine (2%%), gastroenterology (2%), anaesthesiology (1%), intensive care medicine (1%) and neurology (1%). We have added this in the Results section on p 8:

Other fields were obstetrics and gynaecology (7%), oncology (6%), rheumatology (6%), surgery (5%), psychiatry (3%), general medicine (3%), pulmonary medicine (2%), gastroenterology (2%), anaesthesiology (1%), intensive care medicine (1%) and neurology (1%).

For Review Only

Efficacy of experimental treatments compared with standard treatments in non-inferiority trials: A meta-analysis of randomized controlled trials.

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ABSTRACT

Background There is concern that non-inferiority trials might be deliberately designed to conceal that a new treatment is less effective than a standard treatment. To test this hypothesis we performed a meta-analysis of non-inferiority trials to assess the average effect of experimental treatments compared with standard treatments.

Methods One hundred and seventy non-inferiority treatment trials published in 121 core clinical journals were included. Trials were identified in a search of PubMed (1991 to February 20, 2009). Combined relative risk (RR) from meta-analysis comparing experimental with standard treatments was the main outcome measure.

Results The 170 trials contributed a total of 175 independent comparisons of experimental with standard treatments. The combined RR for all 175 comparisons was 0.994 (95% CI 0.978 to 1.010) using a random effects model and 1.002 (95% CI 0.996 to 1.008) using a fixed-effects model. Of the 175 comparisons, experimental treatment was considered to be non-inferior in 130 (74%). The combined relative risk for these 130 comparisons was 0.995 (95% CI 0.983 to 1.006) and the point estimate favoured the experimental treatment in 58% ($n=76$) and standard treatment in 42% ($n=54$). The median non-inferiority margin (RR) pre-specified by trialists was 1.31 (interquartile range [IQR] 1.18 to 1.59).

Conclusion In this meta-analysis of non-inferiority trials the average relative risk comparing experimental with standard treatments was close to 1. The experimental treatments that gain a verdict of non-inferiority in published trials do not appear to be systematically less effective than the standard treatments. Importantly, publication bias and bias in the design and reporting of the studies cannot be ruled out and may have skewed the study results in favour of the experimental treatments. Further studies are required to examine the importance of such bias.

Keywords non-inferiority, meta-analysis, systematic review

INTRODUCTION

Non-inferiority trials are increasingly published in the medical literature, increasingly used in drug licensing, and have at the same time come under increased scrutiny and criticism, up to the allegation that they are unethical.¹⁻¹³ A verdict of “non-inferiority” leaves readers with the impression that a new experimental treatment is as good as an established standard treatment and that the two can be used interchangeably. However, in such trials, non-inferiority is statistically accepted whenever an experimental treatment is unlikely to be worse than an established treatment by more than a pre-specified amount, the so called non-inferiority margin. If a relatively wide margin is chosen, new treatments that are actually less beneficial might wrongly be considered as equally effective. This may lead to acceptance and use of new therapies that are actually less effective in a clinically relevant way.^{10,12}

There is concern that non-inferiority trials might be deliberately designed to conceal that a new treatment is somewhat less effective than a standard treatment.^{10,12} Systematic use of too large non-inferiority margins or systematic biases of design, conduct or reporting of non-inferiority trials may skew results in favour of new treatments.¹⁴⁻¹⁹ In this meta-analysis we examined one type of systematic bias. If trialists systematically compare slightly less effective new treatments to standard treatments, the combined results from a meta-analysis of many trials in which experimental treatments gain a verdict of non-inferiority, would be expected to favour the standard treatment. To test this hypothesis we performed a meta-analysis of non-inferiority trials published in clinical journals and assessed the average effect of experimental treatments compared with standard treatments. Importantly, the combined estimate from the meta-analysis will not be influenced by the choice of the non-inferiority margins.

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METHODS

Eligibility and search strategy

We searched for non-inferiority trials on February 20th 2009 using PubMed (National Library of Medicine) using the text words “noninferiority” or “non inferiority” or “equivalence” combined with the text words “clinical trial” or “trial” or “trials” or “study” or “studies”, limiting the search to publications from 1991 onwards. The initial search was restricted to six general medicine journals (*Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet*, *New England Journal of Medicine* and *PLoS Med*). In a second step the search was extended to include the other 115 journals included in PubMed's selection of core clinical journals (see <http://www.nlm.nih.gov/bsd/aim.html> for a list of these journals). Although equivalence trials (trials that specify both a lower and an upper equivalence margin)^{20,21} were not eligible for inclusion, we included the term equivalence in our search strategy in order not to miss non-inferiority trials that had been described as equivalence trials.

Study selection

All two-arm parallel group non-inferiority trials of an experimental treatment compared with standard therapy were included, independent of the intervention examined in the trial. Articles that were published electronically ahead of print were also considered.

Data extraction

The following information was extracted independently by two investigators (DS, RM): year of publication, journal, subject area (cardiovascular medicine, infectious diseases, obstetrics and gynaecology, rheumatology, surgery or other), primary endpoint, non-inferiority margin for primary endpoint, expected incidence of the primary endpoint in the standard arm, and the point estimate for the comparison of experimental with standard treatment. The primary endpoint was classified into three categories: (i) mortality alone or as part of a combined endpoint, (ii) clinical disease, (iii) surrogate endpoint (imaging or laboratory test).

Disagreements were resolved in consultation with a third investigator (OD). If trials presented more than one primary endpoint, the endpoint for which the sample size had been calculated was used. If it was unclear for which endpoint sample size calculations were done, or if no such calculations were reported, one of the primary endpoints was randomly selected. In trials that included several non-inferiority comparisons using the same standard treatment, for example when testing two dosages of an experimental therapy, one comparison was selected at random and included in the analysis. If a study reported both intention-to-treat- and per-protocol analyses, the result used by the author to determine whether the intervention was non-inferior was extracted. If this was not clear, the per-protocol results were used. The funding source was independently classified by two investigators (DS, OD) as industry, public or mixed funding. The provision of study drugs by industry was considered as a source of industry funding.

Data synthesis and analysis

The confidence intervals and non-inferiority margins reported by the investigators were used to classify the results as superior, non-inferior, inconclusive or inferior according to the definitions given in the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement to non-inferiority trials.⁹ Superiority was assumed if the experimental treatment was significantly ($p < 0.05$) more efficacious than the standard treatment. Non-inferiority was assumed if the 95% confidence interval did not include the non-inferiority margin. Results were classified as inconclusive if the 95% confidence interval included the non-inferiority margin. Treatments were assumed to be inferior if the entire 95% confidence interval was significantly worse than the non-inferiority margin.

Results of comparisons were expressed as ratio measures, which we call relative risks throughout this paper. If the trial reported risk ratios or hazard ratios or odds ratios from statistical models these were used in the analyses. For trials that reported risk differences,

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we calculated the risk ratio. For studies reporting continuous endpoints (for example blood pressure) results were converted to odds ratios using the method described by Hasselblad and Hedges,²² and the odds ratio was then used in further calculations. This method assumes logistic distributions with equal variances in the two treatment groups. Under this assumption the natural logarithm of the odds ratio equals a constant multiplied by the standardized difference between means. If needed, the inverse of the relative risk was calculated, so that ratios above 1 consistently favoured the standard treatment and ratios below 1 favoured the experimental treatment. The relative risks from individual studies were combined using random-effects models. In addition to combining relative risks for all studies, we performed stratified meta-analyses according to whether results were interpreted as inferior, non-inferior or superior, by type of effect measure, by type of endpoint, by source of funding, by journal and according to whether the judgment of the result was based on an intention-to-treat analysis or not. In a random-effects meta-regression model we analyzed the influence of the source of funding.

Pre-specified non-inferiority margins were also expressed as relative risks. Margins that were reported as a difference in incidence were converted to a relative risk by dividing the expected incidence of the primary endpoint in the standard treatment arm plus (for morbidity or mortality) or minus (for beneficial endpoints) the pre-specified margin by the expected incidence of the primary endpoint in the standard treatment arm. For example, if the expected mortality rate in the standard treatment arm was 10% and the pre-specified margin was set at 2%, the margin converted to a relative risk of 1.2 (10 plus 2 divided by 10). Margins could not be expressed as a relative risk for studies that did not report the expected incidence, or studies reporting continuous endpoints. We examined the median and the distribution of non-inferiority margins and examined whether margins differed across the subgroups of trials mentioned above.

We compared the observed incidence of the primary endpoint in the group that received standard treatment with the expected incidence, as specified by the trialists. The result was expressed as a ratio. If needed, the inverse of this ratio was calculated, so that ratios below 1 consistently indicated that the standard treatment performed better than was expected at the design stage of the trial, and ratios above 1 indicated that the standard treatment performed worse than was expected. This ratio could not be calculated for studies that did not report separately the expected, or the observed incidence of the primary endpoint, or studies reporting continuous endpoints.

Statistical analyses were done in Comprehensive Meta-Analysis (version 2.0, Biostat, Englewood, New Jersey, USA) and Stata (version 10.0, Stata Corporation, College Station, Texas, USA).

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RESULTS

Literature search and study characteristics

We identified 532 potentially eligible articles, and excluded 362 studies for the reasons shown in [Figure 1](#). A total of 170 studies which were published in 43 different journals were included (see [Appendix Table 1, 2 and 3](#) for bibliographic details). Five articles reported the results for two separate comparisons. In total, 175 comparisons were therefore included in the analyses. The oldest non-inferiority study in our selection dates from 1993.²³ Seventy-eight percent of included studies date from 2004 onwards reflecting an increase in non-inferiority trials in the last five years.

The characteristics of the 170 non-inferiority trials are described in [Table 1](#). Of the general medical journals, the *New England Journal of Medicine* published the largest number of non-inferiority trials; our search found no non-inferiority trials in *PLoS Medicine*. Most trials were from cardiovascular medicine ($n=47$, 28%) or infectious disease ($n=43$, 25%). Other fields were obstetrics and gynaecology (7%), oncology (6%), rheumatology (6%), surgery (5%), psychiatry (3%), general medicine (3%), pulmonary medicine (2%), gastroenterology (2%), anaesthesiology (1%), intensive care medicine (1%) and neurology (1%). The majority reported risk differences ($n=106$, 61%); 36 studies reported continuous endpoints, which were converted to odds ratios for the present analysis. [Figure 2](#) shows the type of endpoint, number of participants, point estimate, confidence interval and pre-specified margin for 33 comparisons that were reported on the relative risk scale.

For 130 comparisons (74%) we considered the experimental treatment to be non-inferior according to the published criteria.⁹ Of note, in 6 of these 130 comparisons the authors deemed the experimental treatment to be clinically inferior based on a secondary end-point. For 27 comparisons (15%) results were inconclusive, for 15 comparisons (9%) superior and for 3 comparisons (2%) inferior. In 20 instances our assessment differed from the authors'

verdict: in 9 instances we judged the result to be superior where the authors' verdict was non-inferior, in 6 instances to be inconclusive as opposed to inferior and once to be non-inferior instead of inferior. The authors' verdict was more favourable to the experimental treatment in 4 comparisons, each time judging the result to be non-inferior instead of inconclusive.

Meta-analysis

The funnel plot showed a symmetrical distribution of results around relative risk 1 ([Figure 3](#)). Forty-seven percent of comparisons ($n=82$) had a point-estimate above 1 (favouring standard treatment) and 53% ($n=93$) below 1 (favouring experimental treatment). Of the 130 comparisons judged to be non-inferior, the point estimate favoured experimental treatment in 58% ($n=76$) and standard treatment in 42% ($n=54$). The combined relative risk for all 175 comparisons was 0.994 (95% CI 0.978 to 1.010) using a random effects model and 1.002 (95% CI 0.966 to 1.008) using a fixed-effects model. The combined relative risk for comparisons judged to be non-inferior was 0.995 (95% CI 0.983 to 1.006). [Table 2](#) shows stratified random-effects meta-analyses according to trial result, measure of effect, type of endpoint, source of funding, by two journal strata, and according to whether the judgment of the result was based on an intention-to-treat analysis or not. Using a random effects model, the combined estimate for trials funded by industry was 0.978 (95% CI 0.956 to 1.000). The combined result for trials funded by public sources was 1.008 (95% CI 0.980 to 1.038). These two estimates did not differ significantly ($p=0.15$ from random-effects meta-regression). All meta-analyses were also performed using a fixed-effects model and are presented in [Appendix Table 4](#). The main result and the results from the stratified analyses were similar for the random- and fixed-effects meta-analyses except for a difference in the result stratified by funding source.

Non-inferiority margins

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The margin was expressed as a relative risk for 33 comparisons and could be converted from a risk difference to a relative risk for 91 comparisons. The median prespecified non-inferiority margin was 1.31 (IQR 1.18 to 1.59). Stratified according to trial result, the median margin was 1.42 (range 1.21 to 4.75) for 3 comparisons judged to be inferior, 1.33 (IQR 1.14 to 1.51) for 23 comparisons judged to be inconclusive, 1.31 (IQR 1.19 to 1.59) for 92 comparisons judged to be non-inferior and 1.45 (IQR 1.20 to 1.75) for 6 comparisons judged to be superior. Stratified by type of endpoint the median margin was 1.34 (IQR 1.19 to 1.50) for comparisons that had mortality as (part of a combined) endpoint, 1.38 (IQR 1.20 to 1.70) for comparisons in which clinical disease was the endpoint and 1.23 (IQR 1.15 to 1.35) for comparisons reported as a surrogate endpoint. Stratified according to source of funding the median margin was 1.30 (IQR 1.17 to 1.50) for 62 trials funded by industry, 1.31 (IQR 1.12 to 1.63) for 33 trials funded by public sources and 1.35 (IQR 1.23 to 1.55) for 19 trials with mixed funding.

The ratio of the observed and expected incidence of the primary endpoint in the group that received standard treatment could be calculated for 112 comparisons. Fifty-three percent of comparisons ($n=59$) had a ratio below 1, indicating that the standard treatment performed better than was expected at the design stage of the trial and 46% ($n=51$) above 1, indicating that the standard treatment performed worse than was expected. Two ratios were exactly 1. The mean ratio was 0.941 (95% CI 0.859 to 1.030), meaning that on average the chosen standard treatments performed slightly better than was estimated at the design stage of the trials. Stratified by source of funding, this ratio was 0.974 (95% CI 0.865 – 1.097) for 55 studies funded by industry and 0.906 (95% CI 0.760 to 1.080) for 31 studies funded by public sources. These two estimates did not differ significantly ($p=0.5$ from t-test for equality of means).

DISCUSSION

In this meta-analysis of trials using a non-inferiority design, experimental treatments were regarded as non-inferior to standard treatments in the majority of studies. The combined relative risk for these studies comparing experimental with standard treatments was close to 1. For non-inferiority trials published in core clinical journals, this finding contradicts the hypothesis that new treatments that gain a verdict of non-inferiority are systematically less effective than standard treatments.

Our study has several strengths and limitations. We aimed to include all the non-inferiority trials published in these journals, irrespective of the type of endpoints or measures of effect. We restricted the search to the group of core clinical journals, as defined in PubMed, which is the same group of journals as in the Abridged Index Medicus (AIM). This selection covers a wide range of journals from many clinical specialties. Our results may therefore be representative for non-inferiority trials published in other journals. However, external validity may be limited to higher quality journals. If non AIM journals are of lower quality, the characteristics of non-inferiority trials published in those journals might be different. Furthermore, our search would have missed trials that do not mention the non-inferiority design in the abstract, the title or as a key word. The characteristics of such trials might also differ.

We examined two aspects of non-inferiority trials: firstly we combined the results of a large number of non-inferiority trials in a meta-analysis, secondly we examined the non-inferiority margins chosen by the investigators. Importantly, the combined estimate from the meta-analysis will not be influenced by the choice of the non-inferiority margin. The combined estimate will be influenced by the efficaciousness of standard treatment. If the standard treatment is not effective, the experimental treatment is in fact tested against 'placebo' in a non-inferiority design. Although we did not assess whether the chosen standard treatment

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represented the best available comparator, we did assess how standard treatments performed in view of what trialists had expected. On average the standard treatments performed slightly better than was estimated at the design stage of the trials. Our study did not address other important issues pertaining to non-inferiority trials. For example, we did not assess whether a non-inferiority trial was the appropriate design to use (or whether a superiority design would have been more appropriate) or whether the choice of the non-inferiority margin that was used for the power calculation and statistical testing made clinical sense. The non-inferiority margin is often criticized as being arbitrary, unacceptably wide or even fraudulent.^{8 10} The selection of the non-inferiority margin should be based on a combination of statistical reasoning and clinical judgment.^{9,24} Others have reviewed the rationale for the size of the margins in non-inferiority trials.^{7,8} They found that the majority of trials did not justify the choice of the margin and that less than 20% reported a clinical consideration. An in-depth analysis of each trial with subject matter knowledge on each topic would have been required to judge whether the choice of the margin was adequate. This was beyond the aim of the present analysis.

Does our meta-analysis rebuke some of the criticism aimed at non-inferiority trials? We found that the combined relative risk for all studies was close to 1. This contradicts the hypothesis that in non-inferiority trials the experimental treatment is generally less effective than the standard treatment. We believe that this is an important, re-assuring finding, considering the criticism that has been levelled at non-inferiority trials.¹⁻¹² Several issues should nevertheless be considered when interpreting this result. Firstly, current standards for drug approval stipulate that a new treatment should be better than placebo and (at least) non-inferior to the established options. This means that demonstrating non-inferiority can legally suffice for the licensing of a new drug. The underlying assumption is often that a "non-inferior" treatment has added value regarding other properties, such as ease of use, lower costs, or fewer adverse effects, which might offset a small loss in efficacy. Sometimes such superior properties, such as costs, are self-evident and do not have to be

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3 demonstrated in a trial. Claiming that an agent has less adverse effects should however be
4 based on evidence. A separate analysis of the adverse event data, analyses of combined
5 endpoints or a meta-analysis of several trials might be appropriate and informative to
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8 demonstrate superiority in this respect. Of the 175 comparisons in this meta-analysis, we
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10 considered the experimental treatment to be non-inferior in 130 (74%) and superior in 15
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12 (9%). Although in 6 of these 145 comparisons the authors deemed the experimental
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14 treatment to be clinically inferior based on a secondary end-point, the majority of published
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16 non-inferiority trials can be used to support the registration of a new treatment. The added
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18 value and safety of these treatments may not always be self-evident and may not always be
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20 demonstrated in the trial. The follow-up time and the sample size of trials is limited, making it
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22 improbable that rarer side effects or long term side effects are detected. The finding that
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24 studies sponsored by industry were more likely to have results favouring sponsored
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26 treatments is in line with other reports.^{15,25 26} Systematic bias has been suggested as a
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28 possible explanation. Our finding could also be due to the play of chance.
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35 Secondly, for superiority trials it has repeatedly been described how the outcome may be
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37 skewed in favour of the experimental treatment by making convenient choices when
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39 designing the study or reporting or publishing the result. This may involve the choice of (the
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41 dosage of) the comparator drug, the choice of patients, endpoints or of the type of
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43 analysis.^{27 19} It may also involve selective reporting of data or changing the prespecified
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45 endpoint after a study is completed.¹⁶ It is plausible that such mechanisms affect the results
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47 of non-inferiority trials. In other words, biased choices in study design and bias due to
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49 selective reporting of outcomes may make it more likely that an experimental treatment is
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51 considered non-inferior after completion of the trial. We did not have access to the study
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53 protocols of the included articles and relied on what was reported as the primary endpoint.
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55 Also, we restricted our search to studies that have been published. Unpublished trials are
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57 more likely to favour standard treatment.¹⁷ Therefore if publication bias would be an issue,
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59 our results might be skewed in favour of experimental treatments. All these potential sources
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of bias would remain unnoticed in our meta-analysis. Although the funnel plot showed a symmetrical distribution of results around relative risk 1, this does not rule out biases. This leaves the possibility that our finding of an overall relative risk close to unity is skewed in favour of experimental treatment.

Thirdly, the statistical verdict of non-inferiority permits licensing of a drug even if the trial result shows that it is somewhat less effective than standard. Therefore some treatments that are approved based on non-inferiority testing may be less effective compared to the standard therapy with respect to the primary endpoint. A cascade of non-inferiority trials is possible, in which each next experimental treatment is slightly less effective than the previously established “standard”. After several generations of non-inferiority trials ineffective interventions could be licensed, leading to deteriorating patient care.^{4,11} This outcome has been called ‘bio-creep’.²⁸ Our results are relevant in this context. Our study showed that of the 130 comparisons judged to be non-inferior, the point estimate favoured the standard treatment in 42% of trials. Biocreep could occur if two or three trials in succession belong to this 42% category and if each next trial adopts the previous demonstrated non-inferior treatment as the new active control treatment. Importantly, our study provided no empirical evidence for or against the existence of biocreep.

In conclusion, the number of non-inferiority trials published in clinical journals has greatly increased. We found that the experimental treatments that gain a verdict of non-inferiority in trials published in core clinical journals are not systematically less effective than the standard treatments. Biases in design, reporting and publication cannot be ruled out and may have skewed the study results in favour of experimental treatments. Continued vigilance is required to assure that non-inferiority trials are used appropriately.

Figure 1. Summary of the search strategy and study selection.

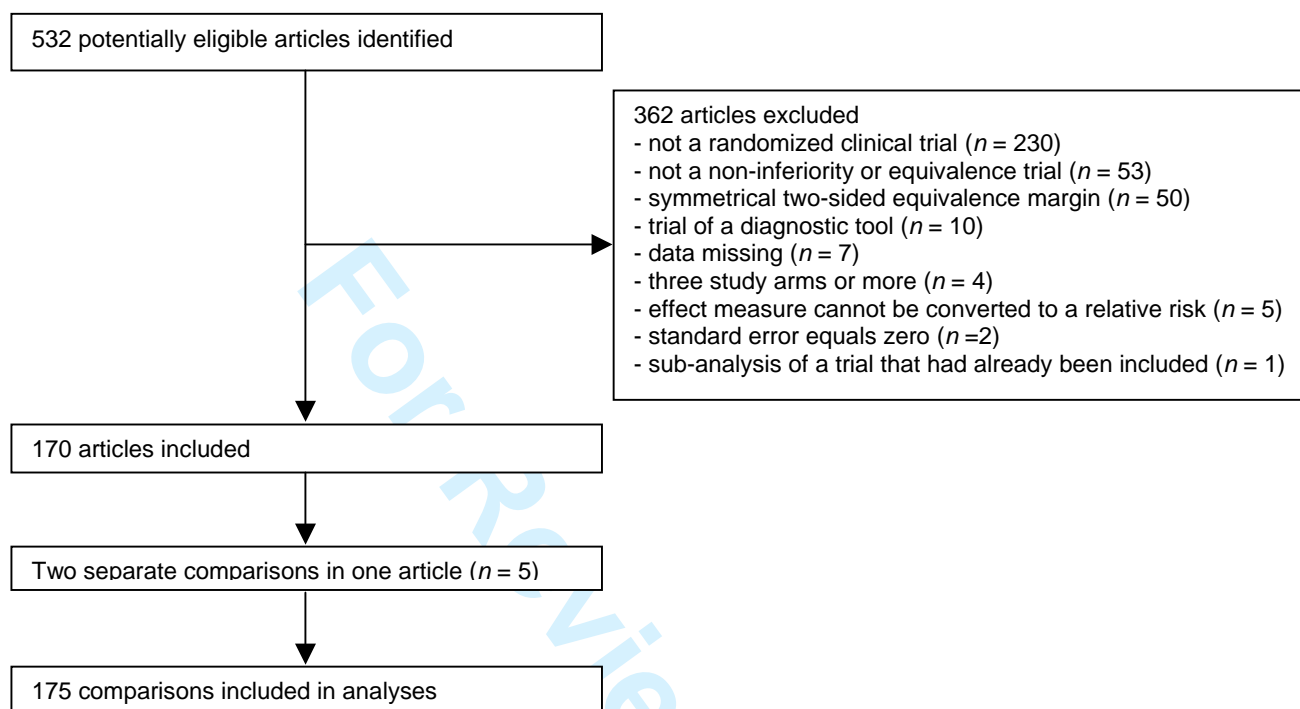


Figure 2. Results for 33 comparisons from 31 trials in which the result was expressed as a relative risk. Point estimates, confidence intervals and non-inferiority margins (red ticks) are shown.

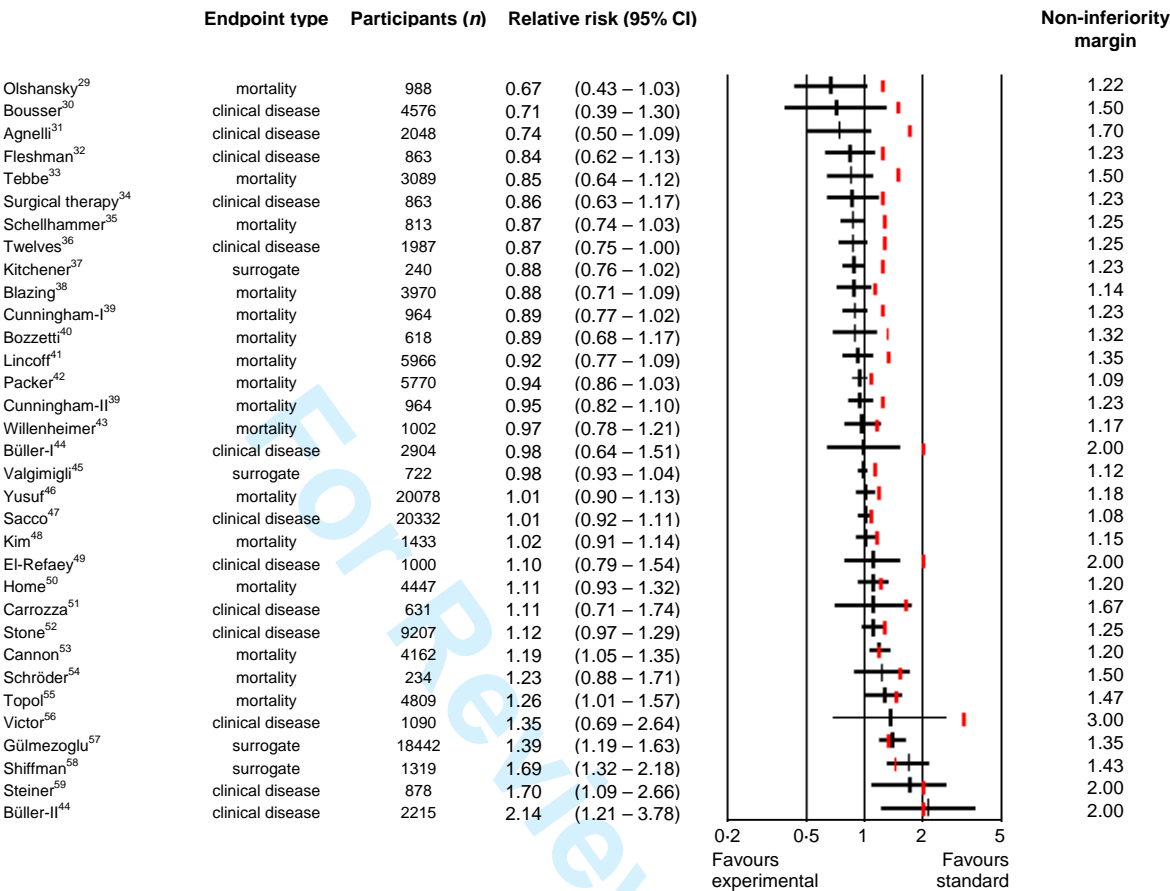
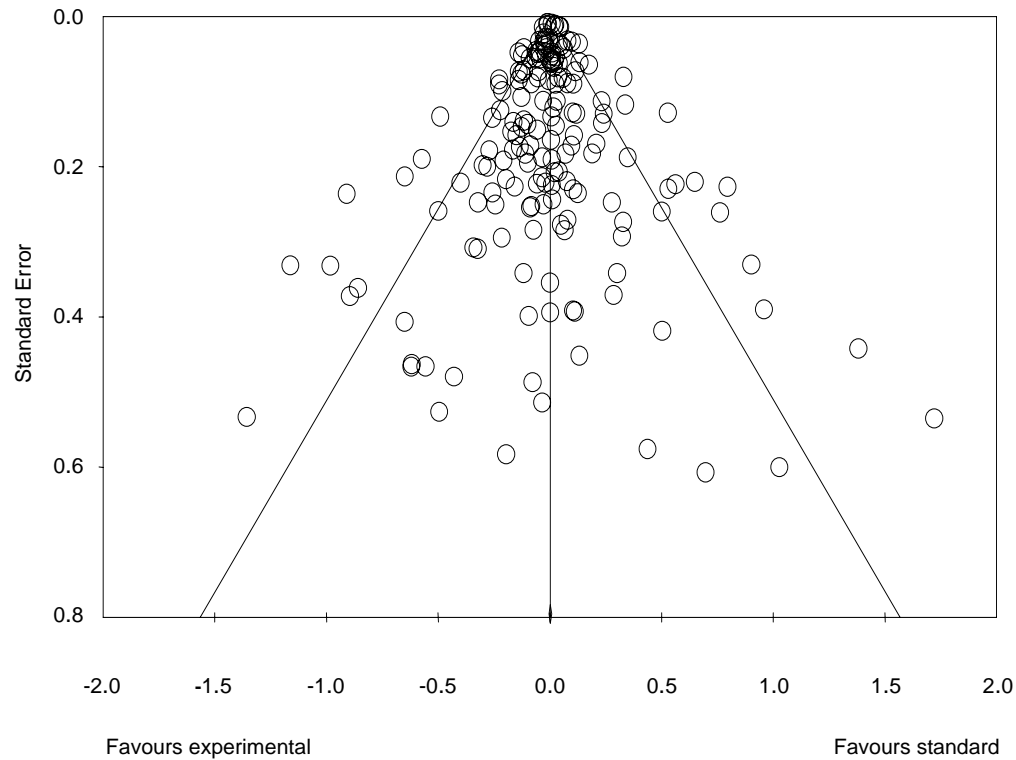


Figure 3. Funnel plot of the standard error by the log relative risk for 175 comparisons.



Treatment on the x-axis and standard error on the y-axis. Bias would lead to an asymmetrical appearance of the funnel plot.

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Table 1. Characteristics of the 170 non-inferiority trials included in the meta-analysis.

Study characteristics	<i>n</i>	%
<i>Journal</i>		
New England Journal of Medicine	33	(19%)
Lancet	28	(16%)
Circulation	11	(6%)
Journal of the American Medical Association	10	(6%)
British Medical Journal	8	(5%)
Obstetrics and Gynaecology	8	(5%)
Paediatrics	8	(5%)
Other (from 36 different journals)	64	(38%)
<i>Field in medicine</i>		
Cardiovascular medicine	47	(28%)
Infectious disease	43	(25%)
Obstetrics and Gynaecology	12	(7%)
Oncology	10	(6%)
Rheumatology	10	(6%)
Surgery	9	(5%)
Psychiatry	5	(3%)
Other	34	(20%)
<i>Type of comparison</i>		
Drug	133	(78%)
Procedure	23	(14%)
Device	14	(8%)
<i>Source of funding</i>		
Industry	94	(55%)
Public or charity	46	(27%)
Mixed	19	(11%)
Not reported	11	(7%)
<i>Median number of participants per comparison (range)*</i>		
	467 (40 to 20332)	
<i>Effect measure*</i>		
Risk difference	106	(61%)
Ratio measure	33	(19%)
Hazard Ratio	20	
Risk Ratio	7	
Odds Ratio	6	
Continuous	36	(21%)
<i>Main analysis used to judge the result*</i>		
Intention-to-treat analysis	95	(54%)
Modified intention-to-treat- or per protocol analysis	80	(46%)

* characteristics for 175 comparisons from the 170 trials.

Table 2. Random-effects meta-analyses of 175 comparisons of experimental and standard treatments from 170 non-inferiority trials.

	Number of comparisons	Relative risk (95% CI)*
Overall analysis	175	0.994 (0.978 - 1.010)
<i>Stratified analyses</i>		
<i>by result</i>		
Result judged as inferior	3	2.255 (1.587 – 3.204)
Result judged as inconclusive	27	1.163 (1.102 - 1.227)
Result judged as non-inferior	130	0.995 (0.983 – 1.006)
Result judged as superior	15	0.694 (0.617 – 0.780)
<i>by effect measure</i>		
Risk difference	106	0.996 (0.982 – 1.010)
Ratio measure	33	1.012 (0.958 – 1.069)
Continuous	36	0.954 (0.826 – 1.101)
<i>by type of endpoint</i>		
Mortality as (part of a combined) endpoint	35	0.974 (0.935 – 1.015)
Clinical disease	81	0.998 (0.980 – 1.017)
Surrogate endpoint	59	1.000 (0.965 – 1.037)
<i>by source of funding</i>		
Industry	96	0.978 (0.956 – 1.000)
Public source	48	1.008 (0.980 – 1.038)
Mixed	20	1.035 (0.972 – 1.103)
Not reported	11	1.018 (0.930 – 1.113)
<i>by journal</i>		
N Engl J Med / Lancet / JAMA / BMJ / Ann Intern Med	87	0.990 (0.968 – 1.012)
Other journals	88	0.999 (0.976 – 1.023)
<i>by the analysis used to judge the result</i>		
Intention-to-treat analysis	95	1.002 (0.977 – 1.028)
Modified intention-to-treat- or per protocol analysis	80	0.989 (0.969 – 1.009)

* All meta-analyses in this table were performed using a random effects model.

All meta-analyses were also performed using a fixed effects model and are presented in *Appendix Table 4*. The main result and the results from the stratified analyses were similar for the random- and fixed-effects meta-analyses except for a difference in the result stratified by funding source.

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KEY MESSAGES

- There is concern that non-inferiority trials might be deliberately designed to conceal that a new treatment is less effective than a standard treatment. There is little empirical evidence at present to support this notion, however.
- The combined relative risk from 170 randomized trials using a non-inferiority design and published in core clinical journals in recent years was close to 1, neither favouring the experimental, nor the standard treatment.
- In the majority of trials, the new treatments were considered to be non-inferior. For these trials the combined relative risk was also close to 1.
- The experimental treatments that gain a verdict of non-inferiority do therefore not appear to be systematically less effective than the standard treatments.
- The evidence from published non-inferiority trials might still be distorted by publication bias, or by a biased choice of standard treatments. Further studies are required to clarify the risk of bias in non-inferiority trials.

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Conflict of interest statement

We declare we have no conflict of interest.

Author's contribution and individual conflict of interest statement

D. Soonawala: "I declare that I participated in the preparation of the protocol, data extraction, data analysis and in writing the manuscript and that I have seen and approved the final version. I have no conflicts of interest. As the corresponding author I had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis and will act as guarantor for the paper"

R.A. Middelburg: "I declare that I participated in the data extraction and that I have seen and approved the final version. I have no conflicts of interest."

M. Egger: "I declare that I participated in the preparation of the protocol, data analysis and in writing the manuscript and that I have seen and approved the final version. I have no conflicts of interest."

J.P. Vandenbroucke: "I declare that I participated in the preparation of the protocol, data extraction, data analysis and in writing the manuscript and that I have seen and approved the final version. I have no conflicts of interest."

O.M. Dekkers: "I declare that I participated in the preparation of the protocol, data extraction, data analysis and in writing the manuscript and that I have seen and approved the final version. I have no conflicts of interest."

Statement regarding the references

D. Soonawala: "I declare that the references have been checked for accuracy and completeness."

This material has not been published previously in a substantively similar form. The manuscript has been carefully edited by M. Egger who has an excellent mastery of the English language.

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