Non-inferiority trials: determining whether alternative treatments are good enough

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ABSTRACT

- New treatments that are potentially as effective as existing treatments are increasingly being developed, some of which may be preferred because of lower cost, fewer side effects, easier administration or less harm.
- Non-inferiority trials attempt to establish whether or not a new treatment — drug or non-drug — is no worse than an established treatment for which efficacy has been determined in placebo-controlled trials.
- Critical issues in the design and conduct of non-inferiority trials include:
  - ➢ defining the acceptable margin of adverse events that, if exceeded, will render the new treatment inferior to the standard treatment (the non-inferiority margin);
  - ➢ calculating the sample size needed to demonstrate non-inferiority;
  - ➢ assessing the robustness of results in terms of absolute versus relative effects, intention-to-treat versus per-protocol analyses, one-sided versus two-sided statistical tests, and observed versus expected event rates for standard treatment;
  - ➢ evaluating all relevant outcomes, including harm; and
  - ➢ stating conclusions that are consistent with aims and results.
- Many non-inferiority trials fail to meet basic quality criteria, report biased and misleading conclusions, and are unduly influenced by commercial sponsors, with some commentators going so far as labelling them unethical.
- Clinicians and trial investigators need to exercise caution when interpreting results of non-inferiority trials which, because they lack a placebo group, can only provide an indirect assessment of the efficacy of a new treatment compared with an existing standard, and where the choice of non-inferiority margin can be highly subjective.

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Most randomised trials are superiority trials, which assess whether a new treatment is more efficacious than a current standard treatment or placebo. However, there is increasing interest in determining whether a new treatment — pharmacological or non-pharmacological — is similar to (equivalent) or no worse than (non-inferior) the standard in terms of efficacy, but preferable owing to lower cost, fewer side effects, easier administration or less harm (Box 1).[1-5] Equivalence and non-inferiority trials assess whether the effects of a new treatment, compared with a standard treatment as the active control, stay within or go beyond a predefined clinically acceptable margin — the equivalence or non-inferiority margin. These study designs are useful in situations where a placebo or no-treatment group is considered unethical, such as treating patients with myocardial infarction, AIDS, tuberculosis or cancer. Another driver is the mandatory requirement of regulatory and licensing agencies for comparisons of new treatments with existing treatments.[6]

In the absence of a placebo control, equivalence and non-inferiority trials rely on certain assumptions:

- Superior efficacy of the standard treatment over placebo has been convincingly proven for a given indication in previous trials.
- Efficacy of the standard treatment will be preserved under the conditions of the equivalence or non-inferiority trial.
- If the new treatment is shown to have equivalent or non-inferior efficacy, then it too would exhibit superior efficacy to placebo if a placebo-controlled trial were to be performed.

These assumptions, and the rationale for equivalence or non-inferiority margins, cannot be validated explicitly. Although new and standard treatments may be shown to be equivalent, they could both be ineffective.

These limitations accentuate the risk of bias in trials that are deficient in design, conduct and reporting. Accordingly, the CONSORT guidelines for randomised trials[7] have recently been extended to cover equivalence and non-inferiority trials.[8] The aim of this review is to highlight the most critical issues that influence validity and generalisability of these trials.

General principles

In superiority trials, a minimum clinically important difference between two treatments is hypothesised and, because the new treatment could be either better or worse than the standard treatment, two-sided statistical tests are used to test the null hypothesis (H_0) of no difference between treatments (Box 2). This difference is usually measured in absolute units (eg, 2 percentage points for a mortality rate or 5 points on a symptom scale), but can be expressed in relative terms (relative risk or odds ratio). The sample size needed to show a difference, if one exists, is calculated from the hypothesised minimum difference, estimates of event rates in the standard treatment group, numbers of participants who might drop out or cross over between treatments, and the chosen level of statistical significance (usually 5%).

In an equivalence trial, a bidirectional equivalence interval is specified and a two-sided test is used to test the null hypothesis that the new treatment is either better or worse than the standard, as revealed by effect estimates lying outside the symmetrical equivalence margins ($-\Delta$ to $+\Delta$). In a non-inferiority trial, the prime interest is determining whether the new treatment is no worse than the non-inferiority margin ($+\Delta$) which, if exceeded, defines the new treatment as being unequivocally inferior. As the difference of interest is in one direction only, one-sided statistical tests can be used to test the null hypothesis that the new treatment is worse than the standard, and, if the statistical chance of this being seen is less than 5%, the alternative hypothesis (H_a) of non-inferiority is accepted.

As no trial is infinitely large, any observed difference between new and standard treatments is an imprecise estimate of the difference. The level of imprecision is denoted by the width of the confidence interval (CI). If the null hypotheses are to be rejected, the upper limit of the CI around the observed difference (ie, the most unfavourable result for the new treatment that is possible given the level of

1 Contemporary examples of randomised equivalence and non-inferiority trials

Disease/condition/ setting	Treatment comparison (new v standard)	Primary efficacy outcome	Putative benefits of new treatment	Efficacy result
Symptomatic carotid artery stenosis[1]	Carotid stenting v carotid endarterectomy	Ipsilateral ischaemic stroke or death at 30 days	Less invasive, less anaesthetic risk, less bleeding, shorter length of stay	Carotid stenting inferior
Empirical antifungal therapy in patients receiving chemo-therapy with neutropenia and persistent fever[2]	Voriconazole v liposomal amphotericin B	Successful treatment*	Less renal and hepatic toxicity, fewer infusion-related reactions, lower cost	Voriconazole inferior
Myocardial infarction complicated by heart failure, left ventricular dysfunction or both[3]	Valsartan v captopril	All-cause mortality at 2 years	More effective blockade of angiotensin II pathway with improved cardiovascular function, fewer side effects	Valsartan not inferior
Diagnosis of pulmonary embolism[4]	Clinical probability assessment, D-dimer and CTPA v same strategy plus venous compression ultrasound of legs	Venous thromboembolic risk at 3 months in patients not treated due to exclusion of pulmonary embolism	Cost and time savings due to omission of ultrasound	Clinical probability assessment, D-dimer and CTPA not inferior
Preoperative assessments[5]	Appropriately trained nurses v interns	Underassessment† possibly affecting perioperative management	Efficiency savings due to substituting interns with nurses	Nurses not inferior

CTPA = computed tomography of pulmonary arteries. * Successful treatment defined as no breakthrough fungal infection, survival 7 days after end of therapy, therapy not discontinued prematurely, fever resolved, and baseline fungal infection resolved. † Underassessment involving history, examination and investigations ordered. ◆

imprecision) should lie within the equivalence margin for equivalence trials, and be less than the non-inferiority margin in non-inferiority trials. The sample size required to avoid rejecting a truly equivalent or non-inferior treatment is again based on the chosen value of the margin in addition to other factors already mentioned for superiority trials.

Elements of a good trial

I will not focus on the well established quality criteria for superiority trials[7,9] that apply equally to equivalence and non-inferiority trials. Here, I will discuss key elements specific to non-inferiority trials (as these increasingly predominate over equivalence trials), with reference to a case study (Box 3).[10-14]

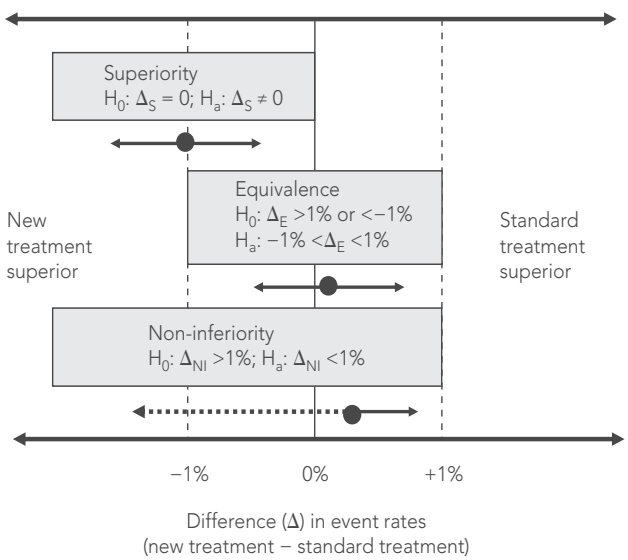
Design

Objectives and outcomes. The study protocol should specify that testing for non-inferiority between two active treatments is one objective — or the only objective — and justify the absence of an inactive control group. Measures of the primary (efficacy) outcome (eg, rates of death or specific clinical events) and of secondary outcomes (eg, costs, side effects, patient adherence, safety) should be clearly defined. In some situations, such as the case study in Box 3, greater safety (eg, fewer major bleeds) at the cost of similar or lower efficacy (eg, fewer strokes) can be assessed as a combined endpoint that measures an adjusted or weighted algebraic trade-off of the two items. The extent to which outcome measures and their methods of ascertainment are similar to those used in the original placebo-controlled trials of standard treatment should also be stated.

Non-inferiority margin. Sound clinical judgement and statistical reasoning are required in defining the non-inferiority margin.

Clinical judgement: the non-inferiority margin should be the smallest clinically meaningful difference between treatments after considering the seriousness of the primary and secondary outcomes. Margins for mortality or disabling events should be more stringent than those for symptom control or quality of life. For serious efficacy endpoints, many experts stipulate that the margin should be no more than 50%, and preferably no more than 20%, of the treatment effect of the

2 Comparison of superiority, equivalence and non-inferiority* hypotheses based on a 2% margin of difference in event rates



H_0 = null hypothesis. H_a = alternative hypothesis.
Δ = difference in event rates between new and standard treatments.
S = Δ in superiority trials. E = Δ in equivalence trials.
NI = Δ in non-inferiority trials.
* Testing for non-inferiority is in one direction only — even if superiority exists (dashed arrow), it is not the hypothesis being tested. ◆

standard treatment, as established in placebo-controlled superiority trials.[15] However, no validated rule for calculating the margin currently exists, and many trials use margins that statisticians regard as too liberal.[16] Wherever possible, the margin should be validated by published expert consensus,[17] and not left to the sole discretion of the investigators and sponsors.

Statistical reasoning: as the magnitude of the standard treatment effect directly influences calculation of the non-inferiority margin, it should be calculated as precisely as possible. Reference should be made to a meta-analysis of all placebo-controlled trials of the standard treatment, in which a summary estimate of effect and its 95% CI are calculated using a random-effects model that demarcates the widest boundaries of uncertainty around the point estimate of effect (Box 4).[18] When individual trials have heterogeneous results, the summary estimate should be expressed in both absolute and relative terms. The non-inferiority margin should preferably be no greater than half of the lower limit of the 95% CI of the standard treatment effect.[15] Extrapolating this treatment effect from historical superiority trials to a non-inferiority trial involves two assumptions. First, the characteristics of the historical trials closely resemble those of the non-inferiority trial — this is termed "constancy". Second, both trials are capable of distinguishing between effective and ineffective treatments — "assay sensitivity". As previously discussed, these assumptions cannot be verified in the absence of a placebo control group.

Sample size. The method for calculating sample size needs to be clearly articulated in the study protocol. Non-inferiority trials usually

3 Case study of two non-inferiority trials

In the treatment of patients with non-valvular atrial fibrillation, the oral direct thrombin inhibitor ximelagatran offers several advantages over warfarin: no need for anticoagulant monitoring, fixed dosing, and less variation in effect with potentially less bleeding risk. Two large clinical trials, one open-label (SPORTIF III)[10] and one double-blind (SPORTIF V)[11] compared the two agents using a non-inferiority design and reported results for the primary efficacy outcome of stroke or systemic thromboembolism (Table). In both studies, the investigators concluded that ximelagatran was as effective as warfarin, but closer inspection of their study design reveals serious deficiencies.

Non-inferiority margin: The margin chosen for both trials was an absolute increase in thromboembolic events of 2% per year. The SPORTIF steering group of 11 members, five of whom were employees of the pharmaceutical sponsor, chose this margin despite citing the results of a meta-analysis of placebo-controlled trials of warfarin in atrial fibrillation that showed, using a fixed-effects model, an absolute reduction in the annual rate of stroke of 3.1%.[12] A subsequent random-effects meta-analysis of the same trials[13] showed a 2.8% decrease in the annual event rate, with a 95% CI of 1.4%–4.2%. Using the liberal 50% rule, the margin should have been no more than half the lower confidence limit: 1.4% ÷ 2 = 0.7%. This is well below the selected margin of 2%. If a more stringent 1% margin had been chosen, the test for non-inferiority would have failed.

Sample size: For SPORTIF V to show non-inferiority at a margin of 1% with 90% power, it would have required a sample size of more than 7000 participants,[14] whereas 3156 were recruited. This low sample size was based on an expected annual event rate for the warfarin group of 3.1%, whereas the observed annual event rate was 1.2%, much closer to the pooled historical annual event rate of 1.9%.

Blinding: SPORTIF III was an open-label trial in which primary endpoints were defined by clinical criteria alone, with no mandatory requirement for confirmatory imaging except angiographic assessment of acute arterial occlusion in patients with pre-existing peripheral vascular disease. In contrast with SPORTIF V, in which patients and clinicians were blind to treatment allocation, PP analysis in SPORTIF III actually showed that ximelagatran had superior efficacy compared with warfarin. However, event rates in the warfarin group in SPORTIF III were more than twice those seen in SPORTIF V (2.9% v 1.2% for ITT analysis; 2.2% v 1.0% for PP analysis), whereas the corresponding rates for ximelagatran were more closely aligned (2.1% v 1.6% and 1.3% v 1.6%). This raises concern about biased analyses in the warfarin group in the unblinded SPORTIF III trial.

Study conduct: Both trials allowed concomitant aspirin therapy of up to 100 mg/day (18% of participants in SPORTIF III; proportion of participants not reported in SPORTIF V), which was not a feature of the historical trials. In SPORTIF III, bleeding risk was increased, more so in the warfarin group, among those receiving aspirin (36% ximelagatran v 52% warfarin) compared with those who did not receive aspirin (24% ximelagatran v 26% warfarin).

Analysis and reporting of results: Although both trials reported ITT and PP analyses in the text, the ITT results were reported as the primary analysis in the abstracts. Also, the study protocols of both trials stipulated that a one-sided 97.5% CI was to be applied (and was indeed used to calculate sample size), but both trials reported only a two-sided 95% CI for the primary outcome. The open-label SPORTIF III trial reported a post-hoc analysis of net clinical benefit that favoured ximelagatran (combined rates of death, primary events and major bleeding per year: 4.6% ximelagatran v 6.1% warfarin; $P = 0.02$), which featured prominently in the abstract. Premature treatment discontinuation was relatively high and unbalanced in both trials (SPORTIF III, 18% ximelagatran v 14% warfarin; SPORTIF V, 33% ximelagatran v 37% warfarin), with no comment on how this may have confounded ITT and PP analyses of low event rates. Neither study repeated analyses using more stringent non-inferiority margins although, in discussion, the SPORTIF V authors mentioned a non-significant non-inferiority result ($P = 0.06$) if a 1% margin was applied. The abstracts of both articles concluded that both drugs were equally efficacious with no reference to non-inferiority being the hypothesis tested.

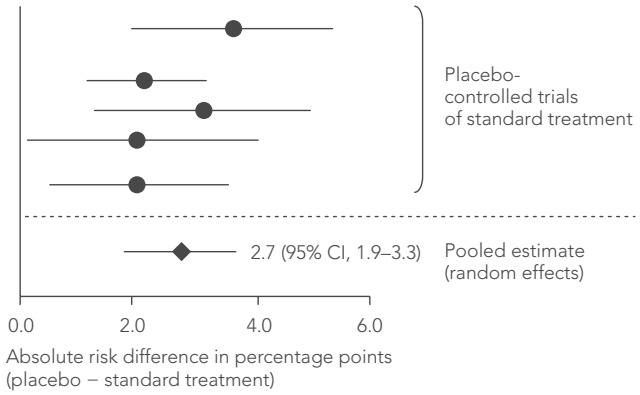
Results from non-inferiority trials comparing ximelagatran with warfarin in patients with non-valvular atrial fibrillation

	Primary efficacy outcome event rate*				
Analysis	Ximelagatran	Warfarin	Difference (95% CI)	*P* for difference	*P* for non-inferiority
SPORTIF III[10]					
ITT	2.1%	2.9%	0.8% (– 0.2% to 1.7%)	0.11	< 0.001
PP	1.3%	2.2%	0.9% (0.2% to 1.7%)	0.02	< 0.001
SPORTIF V[11]					
ITT	1.6%	1.2%	0.4% (– 0.1% to 1.0%)	0.13	< 0.001
PP	1.6%	1.0%	0.6% (– 0.1% to 1.2%)	0.09	< 0.001

SPORTIF = Stroke Prophylaxis Using an Oral Thrombin Inhibitor in Atrial Fibrillation. ITT = intention-to-treat. PP = per-protocol. * Stroke or systemic thromboembolism. ◆

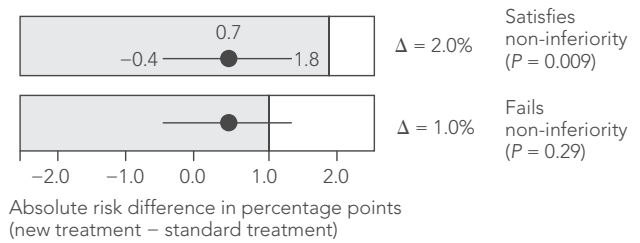
4 Steps in defining the non-inferiority margin

A. Meta-analysis of standard treatment effects reported in historical trials



Standard treatment effects (expressed as absolute risk difference between standard treatment and placebo) obtained from five historical, placebo-controlled trials are pooled, and a summary effect with 95% CI is estimated using random-effects meta-analysis. In this case, the summary effect is 2.7%, with a 95% CI of 1.9%–3.3%.

B. Non-inferiority test of new versus standard treatment



The absolute risk difference between the new treatment and the standard treatment and its two-sided 95% CI is compared with the chosen non-inferiority margin (Δ). In this case, a liberal non-inferiority margin of 2% results in satisfaction of the test for non-inferiority (with highly significant P *value), but a more stringent margin of 1% results in failure to show non-inferiority. The 1% margin is preferable as it equals 50% of the lower confidence limit of the standard treatment effect (1.9%).*

Adapted with permission from: Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med* 2006; 145: 62-69.[18] The American College of Physicians is not responsible for the accuracy of this adaptation. ◆

require larger sample sizes than superiority trials because the non-inferiority margin is smaller than the treatment effects assessed by superiority trials and study power needs to be higher (usually 90%) for a non-inferiority trial, to minimise the risk that a non-inferior treatment is missed due to chance.

Blinding. In contrast to unequivocal endpoints such as death, endpoints requiring subjective interpretation are more vulnerable to bias. In a superiority trial, this bias can be minimised by randomising and concealing allocation and blinding outcome assessors, which makes it impossible to know which participants will be, or were, allocated to a particular treatment. However, no such protection exists in a non-inferiority trial. Even with blinding, investigators could potentially randomly discount a significant proportion of endpoints as not meeting pre-specified event definitions, knowing that this will bias the results towards showing non-inferiority. Unblinded trials with highly subjective endpoints are especially susceptible.[19] Consequently, quality-control procedures and endpoint assessment must be rigorous and at "arms length" from investigators and sponsors.

Study conduct

Fidelity with historical placebo-controlled trials of standard treatment. To ensure no unfair advantage is accorded to the new treatment over the standard, study conduct must closely resemble that of historical trials that compared standard treatment with placebo. Similarities should include patient characteristics, use of the standard treatment (dose, frequency, duration and method of administration), co-interventions, and outcome measures.

Enhancing assay sensitivity. To better distinguish between inferior and non-inferior treatments, investigators should make deliberate efforts to maximise recruitment of patients who are likely to respond to both new and standard treatments in terms of the primary efficacy endpoint and likely to comply with the study protocol. Efforts should also be made to minimise use of non-protocol co-interventions, patient "drop out", and misclassification of outcomes. Some reassurance about assay sensitivity is provided by seeing standard treatment effects of similar magnitude to those in historical trials. Nevertheless, a well executed non-inferiority trial that correctly demonstrates non-inferiority cannot be distinguished, on the basis of outcome data alone, from a poorly executed trial that does not find a true difference.

Analysis and reporting of results

Intention-to-treat versus per-protocol analysis. In superiority trials, intention-to-treat (ITT) analysis of outcomes at study end (ie, according to the treatment group to which participants were originally assigned and irrespective of adherence to study protocol) is preferred to per-protocol (PP) analysis (ie, using outcomes from only those participants who fully complied with the study protocol). This is because ITT analyses yield the most conservative estimate of treatment effect that can be expected in real-world settings, given the inevitability of some patients withdrawing from one or other treatment group because of side effects, crossover to alternative treatment, or refusal to continue. In a non-inferiority trial, ITT analysis is thus more likely to narrow the difference between treatments and yield a non-inferior result. Consequently, a PP analysis is needed to cross-validate the ITT analysis, while bearing in mind substantial variation between treatment groups in rates and reasons for drop-out may also invalidate PP analyses.

Statistical analysis. A non-inferiority trial should specify whether a one- or two-sided CI is placed around the estimate of difference between treatments. If a two-sided test is used, the 95% CI applies; if a one-sided test is used, the 97.5% CI applies. Use of more liberal 90% CIs should be viewed with caution. Ideally, a figure that depicts the CI and non-inferiority margin (or equivalence limits) should be included.

Sensitivity analyses. To assess the robustness of a non-inferiority trial result, data should, where appropriate, be analysed according to absolute versus relative risks, ITT versus PP analyses, and one-sided versus two-sided CIs.

Post-hoc analyses. Both non-inferiority and superiority can be assessed in the same trial without statistical penalty provided the testing of both hypotheses has been pre-specified and the sample size calculated on the basis of the chosen non-inferiority margin, which should be smaller than the superiority margin. Trials that are designed to test a superiority hypothesis but generate non-significant results cannot be re-analysed post-hoc to test for equivalence or non-inferiority.

Interpretation of results. Conclusions should be consistent with study results and expressed with the vocabulary used to define the original trial aims. Ideally, the title of the study report should indicate that a non-inferiority study design was used. Sources of potential bias or imprecision should be discussed, especially those involving secondary outcomes that favour the new treatment.

Critique of equivalence and non-inferiority trials

In general, the rigour of equivalence and non-inferiority trials is suboptimal. In a review of 88 "equivalence" trials published between 1992 and 1996, 67% inappropriately claimed to be equivalence trials, based on non-significant tests of superiority, and only 22% pre-specified equivalence aim, margin and sample size and actually tested the equivalence hypothesis.[20] Eight years later, in a review of 162 trials published during 2003–2004 (46 equivalence; 116 non-inferiority), 93% pre-specified a margin and 78% described sample size calculation.[21] However, only 20% of trials justified the choice of margin, only 43% provided both ITT and PP analyses and only 20% fulfilled all key quality criteria discussed above, and of these, 12% stated misleading conclusions.

Many experts express unease about the validity and ethics of equivalence and non-inferiority trials. Criticisms include false pretexts for non-inferiority testing based on commercial rather than patients' interests, potentially important treatment differences being obscured by liberal non-inferiority margins, unreliable effect estimates based on questionable methods (particularly when standard treatment effects were already small), and betrayal of patient trust by failing to ask and reliably answer important clinical questions.[22] The ethics of not using placebo groups in situations where no standard treatment exists or event rates vary widely has also been challenged.[23] The lack of sound clinical judgement in choosing margins of difference, disparities between initial study protocols and final analyses, inconsistencies in sample size calculation and use of statistical tests, and failure to include appropriate patient populations or deal with potential confounders have also been highlighted.[24,25]

Conclusion

Non-inferiority trials are intended to test that a new treatment is no worse than a standard treatment by more than a pre-specified margin. They have inherent weaknesses that do not apply to superiority trials: no internal demonstration of assay sensitivity; no single, conservative analytical approach; lack of protection from bias by blinding; and difficulty validating arbitrary non-inferiority margins. Although situations exist where the inclusion of placebo control groups may be considered unethical, clinicians should recognise that results of non-inferiority trials are not as credible as those of superiority trials. Such trials should not be performed when standard treatments are not consistently better than placebo (such as antidepressants and antidementia drugs), or when treatment effects are of doubtful clinical relevance.

Competing interests

None identified.

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