Report of Noninferiority and Equivalence Randomized Trials
An Extension of the CONSORT Statement

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The CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed to help authors improve their reporting of randomized controlled trials. Its primary focus was on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another but is now being extended to other trial designs. Noninferiority and equivalence trials have methodological features that differ from superiority trials and present particular difficulties in design, conduct, analysis, and interpretation. Although the rationale for such trials occurs frequently, those designed and described specifically as noninferiority or equivalence trials appear less commonly in the medical literature. The quality of reporting of those that are published is often inadequate. In this article, we present an adapted CONSORT checklist for reporting noninferiority and equivalence trials and provide illustrative examples and explanations for those items amended from the original CONSORT checklist. The intent is to improve reporting of noninferiority and equivalence trials, enabling readers to assess the validity of their results and conclusions.

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For convenience, we will refer to treatments and patients, although we recognize that not all interventions evaluated in RCTs are technically treatments and the participants in trials are not always patients.

Rationale for Noninferiority or Equivalence Designs
Most RCTs aim to determine whether one intervention is superior to another. By contrast, equivalence trials aim to determine whether one (typically new) intervention is therapeutically similar to another, usually an existing treatment. We use new to refer to the treatment under test, and the comparison or reference treatment is often called an active control.

A noninferiority trial seeks to determine whether a new treatment is no
worse than a reference treatment. Because proof of exact equality is impossible, a prestated margin of noninferiority ($\Delta$) for the treatment effect in a primary patient outcome is defined. Equivalence trials are very similar, except that equivalence is defined as the treatment effect being between $-\Delta$ and $\Delta$. True (2-sided) equivalence therapeutic or prophylactic trials are rare because most such trials address the question of noninferiority.

In trials that investigate noninferiority, the question of interest is not symmetric. The new treatment will be recommended if it is similar to or better than an existing one, but not if it is worse (by more than $\Delta$). Superiority of the new treatment would be a bonus. This article focuses mainly on noninferiority trials but applies also to 2-sided equivalence trials.

Noninferiority trials are intended to show whether a new treatment has at least as much efficacy as the standard or is worse by an amount less than $\Delta$, often on the premise that it has some other advantage, eg, greater availability, reduced cost, less invasiveness, or greater ease of administration, for instance, one daily dose rather than 2 doses or more than 2 doses. Some noninferiority trials have been criticized for merely studying a new marketable product (“me-too” drugs).

Noninferiority and equivalence trials are not limited to drugs. For example, a new antenatal care model with fewer clinic visits and reduced cost was investigated for its equivalence to the standard model as regards maternal and neonatal outcomes. A noninferiority trial compared 2 interventional strategies for coronary revascularization in diabetic patients.

**Methodological Issues in Noninferiority and Equivalence Trials**

Noninferiority and equivalence trials present particular difficulties in design, conduct, analysis, and interpretation.

**Hypotheses.** In a superiority trial the null hypothesis is that treatments are equally effective and the alternative hypothesis is that they differ. A type I error is falsely finding a treatment effect when there is none, and a type II error is failing to detect a treatment effect when truly one exists. In noninferiority trials, the null and alternative hypotheses are reversed; a type I error is the erroneous acceptance of an inferior new treatment, whereas a type II error is the erroneous rejection of a truly noninferior treatment.

**Design.** A noninferiority or equivalence trial requires that the reference treatment’s efficacy is established or is in widespread use so that a placebo or untreated control group would be deemed unethical.

Both participants and outcome measures in a noninferiority or equivalence trial should be similar to those in trial(s) that established the efficacy of the reference treatment. Outcome measures should also be similar to those in previous trials.

The required sample size is calculated using the confidence interval (CI) approach, considering where the CI for the treatment effect lies with respect to both the margin of noninferiority $\Delta$ and a null effect. Sample size depends on the level of confidence chosen, the risk of type II error (or desired power), and $\Delta$. A prestated margin of noninferiority $\Delta$ can be specified as a difference in means or proportions or the logarithm of an odds ratio, risk ratio, or hazard ratio. A prestated margin of noninferiority is often chosen as the smallest value that would be a clinically important effect. If relevant, $\Delta$ should be smaller than the “clinically relevant” effect chosen to investigate superiority of reference treatment against placebo. For example, if mortality with treatment A is better than placebo by 10% (absolute difference), a new treatment B might need to be at least 5% better than placebo (and thus no more than 5% worse than A). The required size of noninferiority trials is therefore usually larger than that for superiority trials. Unfortunately, sample sizes for noninferiority and equivalence trials are often too small. Given several previous trials, the effect of the reference treatment can be estimated from a meta-analysis. There are several techniques to determine $\Delta$, its magnitude being influenced by several factors, eg, efficacy, safety, cost, acceptability, and adherence.

**Conduct.** Trial conduct should closely match any trial that demonstrated efficacy of the reference treatment, provided they were of high quality. One should avoid features that might dilute true differences between treatments, thereby enhancing the risk of erroneously concluding noninferiority, eg, poor adherence, drop-outs, recruitment of patients unlikely to respond, and treatment crossovers.

**Analysis.** Although a modified hypothesis testing framework exists, a more informative CI approach is preferred in the design, analysis, and reporting of noninferiority and equivalence trials.

For superiority trials, intention-to-treat (ITT) analysis (analyzing all patients within their randomized groups, regardless of whether they completed allocated treatment) is recommended. Intention-to-treat analysis often leads to smaller observed treatment effects than if all patients had adhered to treatment. In noninferiority trials, ITT analysis will often increase the risk of falsely claiming noninferiority (type I error), although not always. In practice, ITT analysis is often not possible and one uses a “full analysis set” to describe that patient follow-up, which is “as complete... and... close as possible” to ITT.

Alternative analyses that exclude patients not taking allocated treatment or otherwise not protocol-adherent could bias the trial in either direction. The terms on-treatment or per-protocol analysis are often used but may be inadequately defined. Potentially biased non-ITT analysis is less desirable than ITT in superiority trials but may still provide some insight. In noninferiority and equivalence trials, non-ITT...
analyses might be desirable as a protection from ITT’s increase of type I error risk (falsely concluding noninferiority). There is greater confidence in results when the conclusions are consistent.

Subgroup analysis requires the same caveats in noninferiority trials as it requires in superiority trials. Interim analyses in noninferiority trials have some differences in rationale from superiority trials. If noninferiority is established before the trial is completed, there may be no ethical requirement to continue longer because of lack of efficacy. However, other advantages (adverse effects, cost) could justify stopping the trial, to expedite availability of the new treatment. If a treatment is clearly inferior, then stopping the trial (or a particular trial arm) is ethically justified.

**Figure.** Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials

Interpreting a noninferiority trial’s results depends on where the CI for the treatment effect lies relative to both the margin of noninferiority and a null effect. The observed treatment effect is not by itself sufficiently informative. With 2-sided equivalence the interpretation is analogous, but both margins need considering, and claiming equivalence requires the CI to lie wholly between $-\Delta$ and $\Delta$.

Many noninferiority trials based their interpretation on the upper limit of a 1-sided 97.5% CI, which is the same as the upper limit of a 2-sided 95% CI. Although both 1-sided and 2-sided CIs allow for inferences about noninferiority, we suggest that 2-sided CIs are appropriate in most noninferiority trials. If a 1-sided 5% significance level is deemed acceptable for the noninferiority hypothesis test (a decision open to question), a 90% 2-sided CI could then be used. The **Figure** interprets several possible scenarios with 2-sided CIs for a noninferiority trial.

Once noninferiority is evident, it is acceptable to then assess whether the new treatment appears superior to the reference treatment, using an appropriate test or CI (ie, not just the point estimate), preferably defined a priori and with an ITT analysis.

It is inappropriate to claim noninferiority post hoc from a superiority trial unless clearly related to a predefined margin of equivalence. That is, both superiority and noninferiority hypotheses need explicit specification in the trial protocol. It is, however, always reasonable to interpret a CI as excluding an effect of a particular prestated size. Having demonstrated noninferiority against reference treatment, some authors then make claims for efficacy of a new treatment relative to placebo by also using evidence from earlier trials of reference treatment vs placebo. Such inferences assume assay constancy, ie, current and earlier trials are identical in all relevant aspects, eg, participants, outcomes definition, and use of standard therapy. Regarding patient populations, for example, this implies no differences in the effect of treatment across subgroups or similar distribution of relevant subgroups. In the absence of assay constancy, an adjustment method has been proposed. Since assay constancy is inevitably questionable, any claims regarding efficacy of new treatment relative to placebo require cautious interpretation.

**How Common Are Noninferiority and Equivalence Trials?**

Assessing the frequency of noninferiority and equivalence trials is not...
straightforward because of inconsistencies in terminology. A search of the Cochrane Controlled Trials Register in October 2004 for the words *equivalence* or *noninferiority* yielded 1021 of 415 918 trials (0.2%), but these figures are likely to be misleading. Not all noninferiority or equivalence trials use these words, and the term *equivalence* is often inappropriately used when reporting negative results of superiority trials; such trials often lack statistical power to rule out important differences. Identifying noninferiority trials is difficult because they are often labeled as equivalence trials. A recent study found that only 3 of 188 (1.6%) cancer trials in a PubMed electronic search were designed to evaluate equivalence or noninferiority (Luciano Costa, MD, written communication, April 26, 2005).

From the above findings, it seems that whereas the objective of testing for noninferiority or equivalence is likely to be common, there have been relatively few noninferiority and equivalence trials that are both designed and described as such. However, we perceive that these designs are becoming more widespread.

**Quality of Reporting of Noninferiority and Equivalence Trials**

We do not know of a study that looked at reporting of a cohort of trials actually designed as noninferiority or equivalence trials. There have been several reviews of quality of trials claiming equivalence, without differentiation between noninferiority and 2-sided equivalence, because many authors use the term *equivalence* to mean either.

Greene et al identified methodological flaws in a systematic review of 88 studies claiming equivalence, published from 1992 to 1996. Equivalence was inappropriately claimed in 67% of them, on the basis of nonsignificant tests for superiority. Fifty-one percent stated equivalence as an aim, but only 23% were designed with a preset margin of equivalence. Only 22% adopted appropriate practice: a predefined aim of equivalence, a preset $\Delta$, consequent sample size determination, and actually testing equivalence.

Other disease- or field-specific reviews reveal similar findings. Only 2 trials (8%) in a review of 25 RCTs in childhood bacterial meningitis published between 1980 and 2000 that claimed equivalent mortality were designed to test equivalence. A review of 90 RCTs with nonstatistically significant or “negative” results published in 3 surgical journals from 1988 to 1998 found 39% met predefined criteria for establishing equivalence. Only 3 studies in a recent review of 188 cancer trials with negative results used a noninferiority or equivalence analysis. In a review of 20 trials intended to detect equivalence in reproductive health, only 4 stated a margin of equivalence.

McAlister and Sackett evaluated 4 large “negative” RCTs in hypertension as regards methodological requirements for active-control equivalence trials. Only 2 trials published both ITT and per-protocol (or on-treatment) analyses, only 1 trial specified the margin of equivalence in advance, and none was sufficiently large to address the equivalence hypothesis. This illustrates how failure to properly design, conduct, and analyze equivalence trials leads to incorrect conclusions about equivalence.

**Extension of Consort Statement**

To accommodate noninferiority or equivalence trials, an extension of the CONSORT statement should encompass the following issues: (1) the rationale for adopting a noninferiority or equivalence design; (2) how study hypotheses were incorporated into the design; (3) choice of participants, interventions (especially the reference treatment), and outcomes; (4) statistical methods, including sample size calculation; and (5) how the design affects interpretation and conclusions. Consequences for the CONSORT checklist and flow diagram, including specific changes, are described below.

**Checklist**

We build on the work of McAlister and Sackett in modifying the CONSORT checklist, especially items 1 to 7, 12, 16, 17, and 20. New text is shown in italics. For each modification, we include 1 or more examples of good reporting (and further elaboration where appropriate). In some examples, we have added text in brackets to explain the context. We mainly concentrate on noninferiority trials but make some reference to equivalence trials which are much less common.

**Title and Abstract**

**Title and Abstract: Item 1.** How participants were allocated to interventions (eg, random allocation, randomized, or randomly assigned), specifying that the trial is a noninferiority or equivalence trial.

**Title.** “Oral Pristinamycin versus Standard Penicillin Regimen to Treat Erysipelas in Adults: Randomised, Noninferiority, Open Trial”

**Abstract.** “Design—Multicentre, parallel group, open labelled, randomised noninferiority trial.”

**Introduction**

**Background: Item 2.** Scientific background and explanation of rationale, including the rationale for using a noninferiority or equivalence design.

**Example.** “Up to 40 million children worldwide are estimated to suffer from vitamin A deficiency. . . . A dose of 200,000 IU retinyl palmitate to children over 1 year old is most widely used and has generally been regarded as safe and potentially effective. . . . In developing countries, animal products that provide retinyl esters are too expensive. . . . Vegetables and fruit . . . are cheap and good sources of vitamin A in the form of beta carotene. . . . Beta carotene is also considered to be virtually non-toxic. . . . In a preliminary study, . . . after 20 days there was a reversion of the clinical and subclinical signs of vitamin A deficiency in the study group. . . . Since beta carotene is the principal source of vitamin A in developing countries and is
### Table. Checklist of Items for Reporting Noninferiority or Equivalence Trials (Additions or Modifications to the CONSORT Checklist are Shown in Italics)

<table>
<thead>
<tr>
<th>Paper Section and Topic</th>
<th>Item Number</th>
<th>Descriptor (Adapted for Noninferiority or Equivalence Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1*</td>
<td>How participants were allocated to interventions (eg, “random allocation,” “randomized,” or “randomly assigned”), specifying that the trial is a noninferiority or equivalence trial.</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>2*</td>
<td>Scientific background and explanation of rationale, including the rationale for using a noninferiority or equivalence design.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>3*</td>
<td>Eligibility criteria for participants (detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment) and the settings and locations where the data were collected.</td>
</tr>
<tr>
<td>Interventions</td>
<td>4*</td>
<td>Precise details of the interventions intended for each group, detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trial[s] that established efficacy, and how and when they were actually administered.</td>
</tr>
<tr>
<td>Objectives</td>
<td>5*</td>
<td>Specific objectives and hypotheses, including the hypothesis concerning noninferiority or equivalence.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6*</td>
<td>Clearly defined primary and secondary outcome measures, detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).</td>
</tr>
<tr>
<td>Sample size</td>
<td>7*</td>
<td>How sample size was determined, detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice. When applicable, explanation of any interim analyses and stopping rules (and whether related to a noninferiority or equivalence hypothesis).</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence generation</td>
<td>8</td>
<td>Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>9</td>
<td>Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.</td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
<td>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12*</td>
<td>Statistical methods used to compare groups for primary outcome(s), specifying whether a 1- or 2-sided confidence interval approach was used. Methods for additional analyses, such as subgroup analyses and adjusted analyses.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant flow</td>
<td>13</td>
<td>Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>Dates defining the periods of recruitment and follow-up.</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>Baseline demographic and clinical characteristics of each group.</td>
</tr>
<tr>
<td>Numbers analyzed</td>
<td>16*</td>
<td>Number of participants (denominator) in each group included in each analysis and whether “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (eg, 10/20, not 50%).</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17*</td>
<td>For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>All important adverse events or side effects in each intervention group.</td>
</tr>
<tr>
<td>Comment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpretation</td>
<td>20*</td>
<td>Interpretation of the results, taking into account the noninferiority or equivalence hypothesis and any other trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.</td>
</tr>
<tr>
<td>Generalizability</td>
<td>21</td>
<td>Generalizability (external validity) of the trial findings.</td>
</tr>
<tr>
<td>Overall evaluation</td>
<td>22</td>
<td>General interpretation of the results in the context of current evidence.</td>
</tr>
</tbody>
</table>

*Expansion of corresponding item on CONSORT checklist.**

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non-toxic, we compared retinyl palmi-
tate and beta carotene for treatment of
vitamin A deficiency.\textsuperscript{25}

Elaboration. The rationale should cite
evidence for the efficacy of the refer-
ence treatment. If previous trials, or
their systematic review, demonstrate the
superiority of the reference treatment
relative to placebo, they should be cited
with effect sizes and CIs. If no such trials
exist, other evidence for efficacy of the
reference treatment should be given.
Evidence for other advantages of the
new treatment over the reference treat-
ment, if present, should be given, to jus-
tify use of the new treatment, if not in-
favor. One aim of the current trial might
be to provide or support such evi-
dence. In the case of “me-too” drugs,
it should be clear whether there are
other advantages.

Methods

Participants: Item 3. Eligibility crite-
ria for participants (detailing whether
participants in the noninferiority or
equivalence trial are similar to those in
any trial(s) that established efficacy of the
reference treatment) and the settings and
locations where the data were collected.

Example. “From Sept 1, 1992, to Dec
30, 1994, we enrolled 6628 men and
women in 312 health centres in
Sweden . . . who had hypertension
(blood pressure $\geq 180$ mm Hg sys-
tolic, $\geq 105$ mm Hg diastolic, or both),
aged 70-84 years. The only difference
in inclusion criteria between this trial
and the STOP-Hypertension trial was
that patients with isolated systolic hy-
pertension treated with calcium antago-
nists and diuretics were included.”\textsuperscript{27}

Elaboration. Relevant changes in par-
ticipants’ characteristics compared with
previous positive findings in patients with
isolated systolic hypertension treated with
diuretics and calcium antagonists.”\textsuperscript{26}

Elaboration. Relevant changes in par-
ticipants’ characteristics compared with
previous positive findings in patients with
isolated systolic hypertension treated with
diuretics and calcium antagonists.”\textsuperscript{27}

Interventions: Item 4. Precise de-
tails of the interventions intended for
each group, detailing whether the refer-
tence treatment in the noninferiority or
equivalence trial is identical (or very simi-
lar) to that in any trial(s) that estab-
lished efficacy, and how and when they
were actually administered.

Example. “[W]e randomly assigned
women about to deliver vaginally to re-
ceive 600 µg misoprostol orally or 10 IU
oxytocin intravenously or intramuscu-
larly, according to practice . . . The use
of uterotonic agents [oxytocin, a type of
uterotonic, is the reference treatment] in
the management of the third stage of
labour reduces the amount of bleeding and
the need for blood transfusion . . .”\textsuperscript{27}

Elaboration. Any differences be-
tween the control intervention in the trial
and the reference treatment in the pre-
vious trial(s) in which efficacy was es-
established should be reported and
explained. For example, differences may
exist because background treatment and
patient management change with time
and concomitant therapies may differ.\textsuperscript{27}Dose changes may occur: if the dose
of the reference treatment is reduced, it
might result in reduced efficacy; if it is
increased, possibly leading to tolerabil-
ity problems, the new treatment’s ad-
vantages could be overestimated.

Objectives: Item 5. Specific objec-
tives and hypotheses, including the hy-
pothesis concerning noninferiority or
equivalence.

Example. “[A bodyweight-adjusted
single bolus of 0.50-0.55 mg/kg te-
necteplase would be equivalent to a 90
min regimen of alteplase for efficacy and
safety [the primary endpoint for effi-
cacy was all-cause 30-day mortality
from acute myocardial infarction]. In
this double-blind, randomised, con-
trolled study, we formally tested this
hypothesis.”\textsuperscript{13}

Elaboration. The authors should spec-
ify for which outcomes noninferi-
orty or equivalence hypotheses apply
and for which superiority hypotheses
apply. Usually the noninferiority or
equivalence hypothesis refers to the
primary end point, whereas the new
treatment is expected to offer other
advantages, eg, fewer adverse effects,
cost.

Outcomes: Item 6. Clearly defined
primary and secondary outcome mea-
sures, detailing whether the outcomes in
the noninferiority or equivalence trial
are identical (or very similar) to those in
any trial(s) that established efficacy of
the reference treatment and, when
applicable, any methods used to
enhance the quality of measurements
,eg, multiple observations, training of
assessors.

Example. “Over the past decade seven
large, randomised, placebo-controlled
trials involving a total of 16,770 pa-
tients who underwent percutaneous in-
terventions have established that the
overall reduction in the risk of death or
nonfatal myocardial infarction 30 days
after adjunctive inhibition of platelet
glycoprotein IIb/IIIa receptors is 38 per-
cent. Three glycoprotein IIb/IIIa inhibi-
tors were assessed in these trials. The
primary end point [in the present trial]
was a composite of death, nonfatal myo-
cardial infarction, or urgent target-
vessel revascularization within 30 days
after the index procedure.”\textsuperscript{38}

Elaboration. Any differences in out-
come measures in the new trial com-
pared with trial(s) that established ef-
cacy of the reference treatment should
be noted and justified. In particular,
note any changes in timing of evalua-
tion. Ideally, outcomes should remain
unchanged, but often insights do lead
to change as the understanding, man-
gement, and diagnosis of a disease im-
prove. For example, early AIDS trials
used death outcomes, then deaths be-
came uncommon, so they shifted to
AIDS clinical events, then clinical events
became uncommon, so they shifted to
surrogate markers.

Sample Size: Item 7a. How sample
size was determined, detailing whether
it was calculated using a noninferiority
or equivalence criterion, and specifying
the margin of equivalence with the rati-
onde for its choice.

Examples. “Considering previous
studies, a primary event rate of 3.1% per
year was estimated for patients in both treatment groups. To obtain 90% statistical power with a 1-sided $\alpha$ equal to 0.025, approximately 1600 patient-years of exposure per treatment groups are necessary to establish the noninferiority of ximelagatran compared with dose-adjusted warfarin within 2% per year. . . . Assuming an average follow-up of 16 months, approximately 2400 patients are required.”59

“Sample size was based on . . . [an] 8.0% primary quadruple end point event rate in the control (heparin plus Gp IIb/IIIa blockade) group [reference treatment] and a 12.5% relative reduction in the bivalirudin arm. Using a 2-sided $\alpha$ level of 0.05 and 3000 patients per group, the trial had a 99% power to detect superiority over the imputed heparin control [historical control] and a 92% power to satisfy noninferiority criteria relative to heparin plus Gp IIb/IIIa.”46

Elaboration. The margin of noninferiority or equivalence should be specified, and preferably justified on clinical grounds. Its relation to the effect of the reference treatment relative to placebo in any previous trials should be noted (see second example).

Sample size calculations are usually based on the assumption that the point estimate of the difference between treatments will be 0 (as in the first example above). Examples F and G in the Figure would have met the noninferiority criterion had the observed point estimates been 0. That is, the precision of the estimates would have been adequate, had the 2 treatments been equally effective. With a large enough sample, it is possible to demonstrate noninferiority even when the point estimate is between 0 and $\Delta$. If the true effect is assumed to be greater than 0, the sample size will need to be increased, perhaps substantially.

Stopping Rules: Item 7b. When applicable, explanation of any interim analyses and stopping rules (and whether related to a noninferiority or equivalence hypothesis).

Example. “Interim safety analyses were planned when 40 and 70 percent of the total number of women had been enrolled. An increased rate of HIV transmission associated with the shorter regimens, as compared with the long-long regimen, would be considered significant if any of the nominal $P$ values for the differences were less than 0.007 in the first interim analysis and less than 0.012 in the second. . . .”38

Elaboration. It is customary to base interim stopping criteria on $P$ values, and these adjusted $P$ values are analogous to widened CIs.

Statistical Methods: Item 12. Statistical methods used to compare groups for primary outcome(s), specifying whether a 1- or 2-sided confidence interval approach was used. Methods for additional analyses, such as subgroup analyses and adjusted analyses.

Examples. Binary outcome. “The proportion of the intention-to-treat population experiencing primary events per year for both treatment groups, and the associated 1-sided 97.5% CI for the difference, will be estimated using the time to first event. . . . The noninferiority margin ($\Delta$) defined in the primary analysis is based on absolute event rate differences . . . Noninferiority of ximelagatran over warfarin will be accepted [in a 0.025 level test] if the upper bound of the 97.5% CI around the estimated difference in primary event rates lies below $\Delta$. For these studies, an absolute $\Delta$ of 2% was adopted. . . .”59

Continuous outcome. “Regimens were regarded as equivalent if the difference between treatments in change in FEV1 (using 95% CI) was less than 4% of predicted FEV1. . . . Since we were undertaking an equivalence study, the primary analysis was per protocol but an intention-to-treat analysis was also undertaken. The mean difference between treatments and 95% CI for the true difference was obtained from analysis of variance, with adjustment for centre and type of clinic. . . .”15

Elaboration. The upper bound of the 1-sided $(1-\alpha) \times 100\%$ CI (or correspondingly, the upper bound of the 2-sided $(1-\alpha/2) \times 100\%$ CI) for the treatment effect has to be below the margin $\Delta$ to declare that noninferiority has been shown, with a significance level $\alpha$. Both $\Delta$ and $\alpha$ should be prespecified in the noninferiority hypothesis.

Results

Numbers Analyzed: Item 16. Number of participants (denominator) in each group included in each analysis and whether “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (eg, 10/20, not just 50%).

Example. “Efficacy variables were analyzed on an intent-to-treat basis . . . and on an as-treated basis. In the intent-to-treat analysis, patients were considered treatment failures if they made any treatment changes, prematurely discontinued randomized treatment for any reason, or had missing data for 2 consecutive evaluations. In the as-treated analysis, only data from patients continuing randomized treatment were considered for analysis.”60

Outcomes and Estimation: Item 17. For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.

Examples. Inequality of new treatment, figure legend. “Relative risk of blood loss of 1000 mL or more with mifepristone compared with oxytocin [1.39, 95% CI 1.19 to 1.63]. Vertical dotted lines represent margins of clinical equivalence determined a priori [0.74 and 1.35 on the relative scale]. Solid line represents null effect.”37

(A figure similar to case G in the Figure was presented on the relative scale.)

Noninferiority of new treatment. “The primary quadruple composite end point of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding by 30 days occurred in 299 (10.0%) of 2991 patients in the heparin plus Gp IIb/IIIa inhibitor group vs 275 (9.2%) of 2975 patients in the bivalirudin group (OR, 0.92; 95% CI, 0.77-1.09; $P=0.32$). Relative to heparin alone, the imputed

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OR was 0.62 (95% CI, 0.47-0.82), satisfying statistical criteria for non-inferiority to heparin plus GP IIb/IIIa blockade and superiority to heparin alone.46

(A figure similar to case B in the Figure was presented on the relative scale but without the margin of non-inferiority.)

Elaboration. In the first example the new treatment was inferior, but it was uncertain whether the treatment effect was smaller or larger than the margin of equivalence 1.35. The second example demonstrated non-inferiority.

Comment

Interpretation: Item 20. Interpretation of the results, taking into account the non-inferiority or equivalence hypothesis and any other trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.

Examples. Concluding non-inferiority. “According to our definition of equivalence, the efficacy of the . . . long-short regimen (was) statistically equivalent to the efficacy of the long-long regimen . . . The upper limit of the 95 percent confidence interval for the difference between the rates in the two groups was 5.3 percent (close to the boundary of 6.0 percent).”38

Concluding inferiority of new drug (or conventional superiority of reference drug). “Although the trial was intended to assess the non-inferiority of tirofiban as compared with abciximab, the findings demonstrated that tirofiban offered less protection from major ischemic events than did abciximab. . . . In order to meet the present definition of equivalence, the upper bound of the 95% confidence interval of the hazard ratio for the comparison of tirofiban with abciximab had to be less than 1.47. . . . The primary endpoint occurred more frequently among the 2398 patients in the tirofiban group than among the 2411 patients in the abciximab group (7.6 percent vs. 6.0 percent; hazard ratio, 1.26; . . . two-sided 95 percent confidence interval of 1.01 to 1.57, demonstrating the superiority of abciximab over tirofiban; P=0.038).”58

Concluding noninferiority of new drug from a trial designed to assess superiority. “The SYNERGY protocol presupposed that enoxaparin was not demonstrated to be superior to unfracti- nationed heparin, a noninferiority analysis was to be performed. . . . Enoxaparin was not superior to unfractionated heparin but was noninferior for the treatment of high-risk patients with non-ST-segment elevation ACS.”94

Comment

It is not our intent to promote noninferiority or equivalence trials: the design should be appropriate to the question to be answered.23 Available efficacious reference treatments can make use of placebo controls unethical.84 But even in cases for which a treatment is efficacious on some measures, eg, depression scales, it may not be for a rarer but more important outcome, eg, suicide.63 Reports of noninferiority and equivalence trials must be clear enough to allow readers to interpret results reliably. Accordingly, we herein propose extensions to the CONSORT statement to facilitate appropriate reporting of noninferiority and equivalence trials.

We advocate that editors extend support of the original CONSORT statement to include use of this extension to noninferiority and equivalence trials and refer to it in their “Instructions to Authors.” Adoption by journals of the original CONSORT statement is associated with improved quality.63-65 So we hope this proposed extension will result in similar improvements for noninferiority and equivalence trials.

The CONSORT Group continues to update and extend its recommendations. The current recommendations add to recent extensions to cluster randomized trials,66 and the reporting of harms.4 Further extensions are in preparation. The current versions of all CONSORT recommendations are available at http://www.consort-statement.org.

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**CORRECTIONS**

Incorrect Formula: In the Special Communication entitled “Reporting of Non-inferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement” published in the March 8, 2006, issue of JAMA (2006;295:1152-1160), a formula for a 2-sided confidence interval (CI) used to assess noninferiority of a new treatment compared with a standard one with regard to an outcome was incorrect. On page 1158 in the subsection titled “Elaboration” that reads “the upper bound of the 2-sided (1−α/2) × 100% CI for the treatment effect has to be below the margin Δ to declare that noninferiority has been shown . . .” should read “the upper bound of the 2-sided (1−2α) × 100% CI for the treatment effect has to be below the margin Δ to declare that noninferiority has been shown . . .”

Error in Figure: In the Original Contribution entitled “Long-term Renal Outcomes in Patients With Primary Aldosteronism” published in the June 14, 2006, issue of JAMA (2006;295:2638-2645), an error occurred in Figure 3. In the left panel, which reports creatinine clearance values, the scale of the y-axis is not correct, and the data are therefore not plotted correctly. The correct graph appears below.

<table>
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<th>No. of Patients</th>
<th>GFR &lt;105 mL/min per 1.73 m²</th>
<th>GFR ≥105 mL/min per 1.73 m²</th>
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<tr>
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<td>14</td>
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<tr>
<td>Follow-up, y</td>
<td>0 1 2 3 4 5 6 7 8 9</td>
<td></td>
</tr>
</tbody>
</table>

Creatinine Clearance

- ▲ GFR >105 mL/min per 1.73 m²
- ▼ GFR <105 mL/min per 1.73 m²