Reporting of Noninferiority and Equivalence Randomized Trials
Extension of the CONSORT 2010 Statement

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The CONSORT (Consolidated Standards of Reporting Trials) Statement, which includes a checklist and a flow diagram, is a guideline developed to help authors improve the reporting of the findings from randomized controlled trials. It was updated most recently in 2010. Its primary focus is on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another. The CONSORT Statement has been extended to other trial designs such as cluster randomization, and recommendations for noninferiority and equivalence trials were made in 2006. In this article, we present an updated extension of the CONSORT checklist for reporting noninferiority and equivalence trials, based on the 2010 version of the CONSORT Statement and the 2008 CONSORT Statement for the reporting of abstracts, and provide illustrative examples and explanations for those items that differ from the main 2010 CONSORT checklist. The intent is to improve reporting of noninferiority and equivalence trials, enabling readers to assess the reliability of their results and conclusions.

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THE ORIGINAL CONSORT (Consolidated Standards of Reporting Trials) Statement was developed to help alleviate the problem of inadequate reporting of randomized controlled trials (RCTs).[1-3] The statement, recently updated as CONSORT 2010,[4,5] comprises evidence-based recommendations for reporting RCTs, including a diagram showing the flow of participants through the trial.

The initial focus of the CONSORT Statement was on parallel-group trials,[1-3] aiming to identify treatment superiority if it exists. Most CONSORT recommendations apply equally to other trial designs, but some need adaptation. We therefore extended the CONSORT recommendations to noninferiority and equivalence trials in 2006.[6] The present article updates those recommendations to reflect the new CONSORT 2010 Statement and the 2008 CONSORT Statement for the reporting of abstracts, together with recent methodological publications.[7,8] The main changes from the 2006 article are shown in the Box. We generally focus on noninferiority trials throughout, but the same principles apply to equivalence trials.

First, the article explains the rationale for such trials. Second, it considers

ers how commonly noninferiority trials are published. Third, it provides empirical evidence about their quality. Fourth, it explains the approach used to update the CONSORT Statement to include noninferiority trials. Fifth, it presents the updated CONSORT checklist for reporting noninferiority trials and provides illustrative examples (and further elaboration) for those items that have been amended.

For convenience, the article will refer to treatments and patients, although 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. Failure to show a difference does not mean they are equivalent. By contrast, equivalence trials[10] 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 evaluation, and the comparison or standard or reference treatment is often called an "active control." We will generally use the term "reference treatment" for consistency.

A noninferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable amount.

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Because proof of exact equivalence is impossible, a prestated margin of noninferiority (Δ) 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 $+\Delta$. For therapeutic or prophylactic trials the noninferiority approach is much more common than a true (2-sided) equivalence approach. However, equivalence trials are more common in pharmacokinetics, in which a difference in either direction from the reference treatment is of importance.

Noninferiority of the new treatment with respect to the reference treatment is of interest on the premise that the new treatment has some other advantage, such as greater availability, reduced cost, less invasiveness,[11,12] fewer adverse effects (harms),[13] or greater ease of administration.[14] In trials that investigate noninferiority, therefore, the question of interest is not symmetric.[15] The new treatment will be recommended if it is similar to the reference treatment for a prespecified primary outcome but not if it is worse by more than Δ. Superiority of the new treatment for the primary outcome would be an additional benefit. Some noninferiority trials have been criticized for merely studying a new marketable product ("me-too" drugs) without offering any advantages over existing products.[16] The use of noninferiority or equivalence trials has been criticized on the grounds that they ask "no relevant clinical questions" and are therefore unethical.[17] But some observers argue that this view is misplaced.[18,19]

This article focuses mainly on noninferiority trials but applies also to the less common 2-sided equivalence trials (eAppendix, available at http://www.jama.com).

How Common Are Noninferiority Trials?

Assessing the frequency of noninferiority trials is complicated, because not all noninferiority or equivalence trials use these words, and the term "equivalence" is often inappropriately used

when reporting "negative" (null) results of superiority trials; such trials often lack statistical power to rule out important differences.[20,21]

A recent review of 583 noninferiority trials of drug therapies published between 1989 and 2009 showed an increasing trend, with only 1 trial published before 1999 and more than 100 trials published per year from 2007.[22] A third of these were in the fields of infectious diseases or cardiology. An earlier review found the same 2 specialties had the greatest number of noninferiority and equivalence trials.[23] Surveys in ophthalmology[24] and oncology[25] also found increases in the number of such trials.

Quality of Reporting of Noninferiority Trials

Early reviews of the quality of trials claiming equivalence found that important deficiencies were common. Equivalence was inappropriately claimed in 67% of 88 studies published from 1992 to 1996 on the basis of nonsignificant tests for superiority.[21] Fifty-one percent stated equivalence as an aim, but only 23% reported that they were designed with a preset margin of equivalence. Other disease- or field-specific reviews had similar findings.[26-29]

More recent reviews have found that the quality of reports of noninferiority and equivalence trials remains poor. In one review (covering the years 1990 to 2000) only about one-fifth of 332 noninferiority and equivalence trials provided a suitable rationale for the noninferiority margin.[23] In another review covering noninferiority trials indexed in PubMed as of February 5, 2009, almost all of 232 published reports of equivalence and noninferiority drug trials specified the noninferiority margin, but only 24% explained how it was determined.[30,31] Other reviews had broadly similar findings.[32-34] An increasing quality of reporting of noninferiority trials in oncology was observed from 2001 to 2010.[35]

Updating the CONSORT Statement Extension for Noninferiority Randomized Trials

The updated CONSORT 2010 Statement comprises a 25-item checklist and a participant flow diagram.[4] In the 2010 update, some new items and subitems were introduced, wording was simplified and clarified, and the specificity of some items was made more explicit by breaking them into subitems. Methodological advances reported in the literature since the 2001 Statement were reviewed and taken into consideration. This noninferiority extension was undertaken to reflect the updated CONSORT Statement and to integrate any significant advances in noninferiority trials methodology since 2006.

The Updating Process

An electronic search of publications citing the original CONSORT extension for noninferiority and equivalence trials[6] was conducted using Web of Science (October 14, 2010). The search yielded 260 publications. An initial assessment of the titles and abstracts was made for relevance, yielding 142 articles. After excluding repeated publications, 137 articles remained, of which 85 were trial reports, 47 were methodological papers, and 5 were reviews of published reports of trials potentially relevant to the update of the CONSORT extension. The methodological studies and reviews were assessed for material that might influence the update. In addition, we reviewed publications from 2006 and later, including guidelines issued by both the Food and Drug Administration[36] and the European Medicines Agency[37,38] for sponsors to consider when designing and reporting noninferiority trials (whether for prelicensing pivotal trials or postlicensing safety trials). The citation search was rerun on October 8, 2012, from which an additional 149 articles were considered for relevance.

Three authors (G.P., D.R.E., D.G.A.) met face to face on several occasions to discuss the revision of the extension and also discussed multiple drafts on conference calls and by e-mail. A draft of the revised checklist and accompanying text was distributed to other coauthors, and the subsequent revision was circulated to the larger CONSORT group for feedback. After consideration of their comments the final version was prepared and approved by the CONSORT Executive (http://www.consort-statement.org /about-consort/the-consort-group /the-consort-group-executive/).

Methodology

Methodological considerations in noninferiority trials are discussed in the eAppendix. Key issues include the need to state the trial hypotheses in relation to the noninferiority margin; the choice of this margin; analysis using a CI approach; and the presentation and interpretation of the results using the CI in relation to the noninferiority margin (FIGURE 1).

Revised Extension of CONSORT Statement

To accommodate noninferiority trials, an extension of the CONSORT Statement should encompass the following main issues: (1) the rationale for adopting a noninferiority 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, including specific changes, are described below. The flow diagram was not considered to require any specific modification.

Checklist

The revised checklist for the reporting of noninferiority trials, updated in line with the CONSORT 2010 Statement,[4] is presented in TABLE 1. This checklist relates to noninferiority trials, but the same issues apply to equivalence trials.

We have reformatted the checklist in line with the style currently promoted by the CONSORT Group, as used for the extensions for nonpharmacological interventions, pragmatic trials, and cluster randomized trials.[39-41] We show the text in 2 columns, the first comprising the CONSORT 2010 checklist and the second the revised extension for noninferiority trials. Several items are extended to cover reporting recommendations specific to the noninferiority design.

For each extended item, we include 1 or more examples of good reporting and

Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials

Treatment Difference for Adverse Outcome
(New Treatment Minus Reference Treatment)
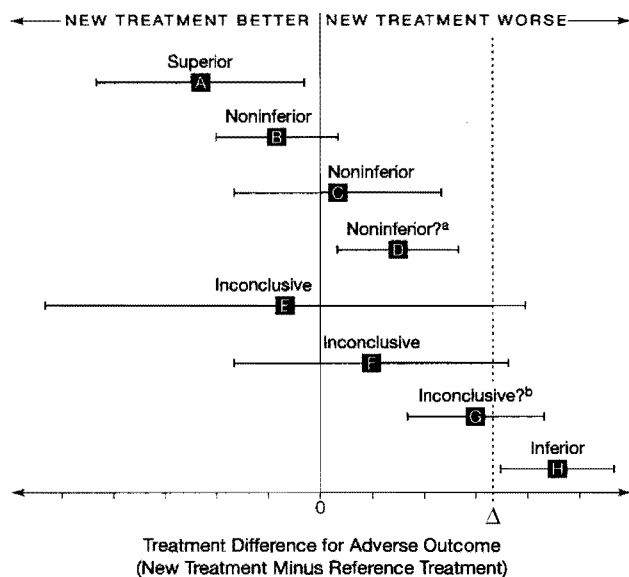
Error bars indicate 2-sided 95% CIs. The blue dashed line at $x=\Delta$ indicates the noninferiority margin; the blue tinted region to the left of $x=\Delta$ indicates the zone of inferiority. A, If the CI lies wholly to the left of zero, the new treatment is superior. B and C, If the CI lies to the left of Δ and includes zero, the new treatment is noninferior but not shown to be superior. D, If the CI lies wholly to the left of Δ and wholly to the right of zero, the new treatment is noninferior in the sense already defined but also inferior in the sense that a null treatment difference is excluded. This puzzling circumstance is rare, because it requires a very large sample size. It also can result from a noninferiority margin that is too wide. E and F, If the CI includes Δ and zero, the difference is nonsignificant but the result regarding noninferiority is inconclusive. G, If the CI includes Δ and is wholly to the right of zero, the difference is statistically significant but the result is inconclusive regarding possible inferiority of magnitude Δ or worse. H, If the CI is wholly above Δ, the new treatment is inferior.
[a] This CI indicates noninferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.
[b] This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard. Adapted from Piaggio et al.[6]

Table 1. Information to Include When Reporting a Noninferiority or Equivalence Randomized Trial: Extension of CONSORT 2010 Checklist[a]

Section/Topic	Item No.	Standard CONSORT 2010 Checklist Item	Extension for Noninferiority Trials
		Title and Abstract	
Title	1a	Identification as a randomized trial in the title	Identification as a noninferiority randomized trial in the title
Abstract	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[7,8])	See Table 2
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a noninferiority design
	2b	Specific objectives or hypotheses	Hypotheses concerning noninferiority, specifying the noninferiority margin with the rationale for its choice
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	Whether participants in the noninferiority trial are similar to those in any trial(s) that established efficacy of the reference treatment
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether the reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Specify the noninferiority outcome(s) and whether hypotheses for main and secondary outcome(s) are noninferiority or superiority. Whether the outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	Whether the sample size was calculated using a noninferiority criterion and, if so, what the noninferiority margin was
	7b	When applicable, explanation of any interim analyses and stopping guidelines	To which outcome(s) they apply and whether related to a noninferiority hypothesis
		Randomization	
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Whether a 1- or 2-sided confidence interval approach was used
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
No. analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, the estimated effect size, and its precision (such as 95% confidence interval)	For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin may be useful
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	

(continued)

Table 1. Information to Include When Reporting a Noninferiority or Equivalence Randomized Trial: Extension of CONSORT 2010 Checklist[a] (continued)

Section/Topic	Item No.	Standard CONSORT 2010 Checklist Item	Extension for Noninferiority Trials
		Results	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[26])	
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Interpret results in relation to the noninferiority hypothesis. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, provide justification for switching
		Other Information	
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a] This checklist relates to noninferiority trials, but the same issues apply to equivalence trials. The Consolidated Standards of ReportingTrials (CONSORT) Group "strongly recommends reading this checklist in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items."[5] This checklist may be republished without restriction.

provide explanatory text. In some of the examples we have added text in brackets to explain the context. In some cases, a particular item is well reported, but providing an example does not imply that all aspects are well reported. For some items it was not possible to find a perfectly reported example. Throughout the literature, authors use different pairs of comparative terms (eg, greater than/less than, better/worse) to characterize the direction of effects, depending on whether the end points are positive (eg, survival) or negative (eg, adverse events). We have not changed the original text of each example but tried to clarify the meaning of the comparative terms used, where it might be confusing.

Title and Abstract

Item 1a: Title. *Standard CONSORT item*: Identification as a randomized trial in the title. *Extension for noninferiority trials*: Identification as a noninferiority randomized trial in the title.

Example. "Dabigatran Etexilate Versus Enoxaparin for Prevention of Venous Thromboembolism After Total Hip Replacement: A Randomised, Double-Blind, Non-Inferiority Trial."[42]

Explanation. Readers should be able to easily identify from the title or abstract that the study was a noninferiority or equivalence randomized trial. In-

cluding the design in the title or abstract also ensures ease of identification of these studies in a literature search for inclusion in systematic reviews.

Item 1b: Abstract. *Standard CONSORT item*: Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[7,8]). *Extension for noninferiority trials*: See TABLE 2.

Example. This example details only those parts relevant to noninferiority.[43]

TITLE: IDENTIFICATION OF STUDY AS A NONINFERIORITY TRIAL. "Duloxetine, Pregabalin, and Duloxetine plus Gabapentin for Diabetic Peripheral Neuropathic Pain Management in Patients With Inadequate Pain Response to Gabapentin: An Open-Label, Randomized, Noninferiority Comparison."

METHODS-OBJECTIVE: SPECIFIC HYPOTHESIS CONCERNING NONINFERIORITY, INCLUDING NONINFERIORITY MARGIN. "To determine whether duloxetine is noninferior to (as good as) pregabalin in the treatment of pain associated with diabetic peripheral neuropathy. . . . Noninferiority would be declared if the mean improvement [in the weekly mean of the diary-based daily pain score] for duloxetine was no worse than the mean improvement for pregabalin, within statistical variability, by a margin of −0.8 unit."

METHODS-OUTCOME: CLARIFY FOR ALL REPORTED OUTCOMES WHETHER NONINFERIORITY OR SUPERIORITY. "The primary objective was a noninferiority comparison between duloxetine and pregabalin on improvement in the weekly mean of the diary-based daily pain score (0- to 10-point scale) at end point.

" . . . adverse effects, nausea, insomnia, hyperhidrosis, and decreased appetite [were secondary outcomes to be assessed for superiority]."

RESULTS-OUTCOME: FOR THE PRIMARY NONINFERIORITY OUTCOME, RESULTS IN RELATION TO NONINFERIORITY MARGIN. "The 97.5% lower confidence limit was a −0.05 difference in means, establishing noninferiority."

CONCLUSIONS: INTERPRETATION TAKING INTO ACCOUNT THE NONINFERIORITY HYPOTHESES AND ANY SUPERIORITY HYPOTHESES. "Duloxetine was noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin."

Explanation. Clear, transparent, and sufficiently detailed abstracts are important. Readers may only have access to the abstract, and many others skim it before deciding whether to read further. A well-written abstract also helps in retrieval of relevant reports from elec-

tronic databases. In 2008, a CONSORT extension for reporting abstracts was published,[7,8] and those recommendations were incorporated into CONSORT 2010. For noninferiority studies, the study design[24] and the noninferiority margin[32] are poorly reported in abstracts. In addition to the items recommended for all trials, abstracts for noninferiority RCTs should specify the noninferiority hypothesis, identify the primary outcome and noninferiority margin, and make clear whether hypotheses for other reported outcomes are noninferiority or superiority. The results should relate the primary noninferiority outcome to the noninferiority margin. The overall interpretation should take account of noninferiority and also any superiority hypotheses (Table 2).

Introduction

Item 2a: Background. *Standard CONSORT item:* Scientific background and explanation of rationale. *Extension for noninferiority trials:* Rationale for using a noninferiority design.

Example. "German guidelines consider adjuvant fluorouracil the standard of care [for locally advanced rectal cancer]. Optimisation of local tumour control has meant that distant metastases now represent the most common type of treatment failure in rectal cancer. . . . Capecitabine is an oral fluoropyrimidine derivative that was as effective as fluorouracil plus folinic acid for adjuvant treatment of stage III colon cancer. It was also non-inferior to infusional fluorouracil in combination with oxaliplatin for first-line treatment of metastatic colorectal cancer . . . no randomised trial has compared capecitabine with perioperative fluorouracil in locally advanced disease. Our choice of a non-inferiority trial design was based on the expectation that non-inferiority of capecitabine, given orally on an outpatient basis, would be sufficient to tip the risk-benefit ratio in its favour."[44]

Explanation. The rationale for using a noninferiority design should include evidence for the efficacy of the reference treatment in a similar context. If previous trials (preferably as part of a systematic review) demonstrated the superiority of the reference treatment relative to placebo (or an equivalent, such as "usual care" for nonpharmacological interventions) they should be cited, preferably with effect sizes and CIs. If no such trials exist, other evidence for efficacy of the reference treatment should be given. Evidence for other potential advantages of the new treatment over the reference treatment should be summarized, to justify use of the new treatment if it should be shown to be noninferior. One aim of the current trial might be to provide or support such evidence. (See also checklist items 4a, 5, and 6.)

Item 2b: Objectives. *Standard CONSORT item:* Specific objectives or hypotheses. *Extension for noninferiority trials:* Hypotheses concerning noninferiority, specifying the noninferiority margin with the rationale for its choice.

Example. "A sequential analysis for the antiplatelet comparison was developed and planned to first test the noninferiority of aspirin plus extended-release dipyridamole as compared with clopidogrel. If this condition was sat-

Table 2. Information to Include in the Abstract of a Report of a Noninferiority or Equivalence Randomized Trial: Extension of CONSORT for Abstracts Checklist[7,8a,b]

Item	Standard Checklist Item	Extension for Noninferiority Trials
Title	Identification of study as randomized	Identification of study as a noninferiority trial
Trial design	Description of the trial design (eg, parallel, cluster, noninferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings in which the data were collected	
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	Specific hypothesis concerning noninferiority, including noninferiority margin
Outcome	Clearly defined primary outcome for this report	Clarify for all reported outcomes whether noninferiority or superiority
Randomization	How participants were allocated to interventions	
Blinding (masking)	Whether participants, caregivers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	
Recruitment	Trial status	
Numbers analyzed	Number of participants analyzed in each group	
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	For the primary noninferiority outcome, results in relation to noninferiority margin
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	Interpretation taking into account the noninferiority hypotheses and any superiority hypotheses
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

Abbreviation: CONSORT, Consolidated Standards of Reporting Trials.
[a]This checklist relates to noninferiority trials, but the same issues apply to equivalence trials.
[b]This checklist may be republished without restriction.

isfied, then the superiority of aspirin plus extended-release dipyridamole over clopidogrel could be assessed in a second test of the conventional null hypothesis of no difference between the two treatments.

Confirmation of noninferiority in this trial involved the prespecification of a hazard ratio for aspirin plus extended-release dipyridamole, as compared with clopidogrel, that is below a predefined margin. The margin was defined in the following way. . . . "[45] (See item 7a.)

Explanation. The authors should specify for which outcomes noninferiority hypotheses apply and for which superiority hypotheses apply. Usually the noninferiority hypothesis refers to the primary end point, whereas the new treatment is expected to offer other advantages, eg, fewer adverse effects or lower cost. If the trial is multigroup or the treatments have a factorial structure, the comparisons to which the noninferiority hypothesis applies should be specified. If sequential testing of noninferiority and superiority hypotheses was planned, that should also be reported.

The rationale for the choice of the noninferiority margin and whether the margin is based on a relative or absolute scale should be specified because relative measures tend to make it less easy to conclude noninferiority, particularly when observed rates turn out to be smaller than the expected rates.[46,47]

The method used to set the margin of noninferiority should be reported. Conventionally, the margin is taken as the size of the effect considered clinically irrelevant. That approach might show an ineffective new treatment as noninferior if the margin is too large in relation to the effect of the reference treatment compared with placebo. To prove that the new treatment is effective, the effect retention or putative placebo method has been proposed (eAppendix),[36] and it should be used if possible if the noninferiority trial is aimed for drug approval.[35,47]

METHODS

Item 4a: Participants. *Standard CONSORT item:* Eligibility criteria for participants. *Extension for noninferiority trials:* Whether participants in the noninferiority trial are similar to those in any trial(s) that established efficacy of the reference treatment.

Example. "[We] enrolled 6628 men and women in 312 health centres in Sweden . . . who had hypertension (blood pressure ≥ 180 mm Hg systolic, ≥ 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 hypertension could be included in STOP Hypertension-2, based on previous positive findings in patients with isolated systolic hypertension treated with diuretics and calcium antagonists."[48]

Explanation. Because an inference of noninferiority relies on evidence that the reference treatment is effective (see "Assay Sensitivity" in eAppendix), relevant differences in participants' characteristics compared with previous trials should be reported and explained. Such description should concentrate on differences that might affect response to treatments. For continuous variables it is important to provide not just the mean values but also an indication of variability (eg, standard deviation).

Item 5: Interventions. *Standard CONSORT item:* The interventions for each group with sufficient details to allow replication, including how and when they were actually administered. *Extension for noninferiority trials:* Whether the reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy.

Example. "The current international definition [of active management of the third stage of labour (AMTSL)] comprises: administration of oxytocin soon after delivery of the baby; controlled cord traction; and uterine massage after delivery of the placenta. . . . Randomised trials of [AMTSL] . . . included early clamping and cutting of the cord [full package, the reference treatment]. The experimental intervention assessed in the trial was the simplified package, in which placental delivery was allowed to occur with the aid of gravity and maternal effort [full package without controlled cord traction]. The full package practised in the trial was similar to the way it has been executed in other AMTSL trials except for delayed cord clamping."[49]

Explanation. Any differences between the control intervention in the current trial and in the previous trial(s) in which efficacy was established should be reported and explained. For example, differences may exist because patient management changes with time and concomitant therapies may differ.[50] Doses may differ: if the dose of the reference treatment is reduced, it might result in reduced efficacy; if it is increased, possibly leading to tolerability problems, the advantages of the new treatment could be overestimated.

Item 6a: Outcomes. *Standard CONSORT item:* Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed. *Extension for noninferiority trials:* Specify the noninferiority outcome(s) and whether hypotheses for main and secondary outcome(s) are noninferiority or superiority. Whether the outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment.

Example. "[S]even large, randomised, placebo-controlled trials involving a total of 16,770 patients who underwent percutaneous interventions 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 percent [relative reduction]. . . . The primary end point [in the present trial] was a composite of death, nonfatal myocardial infarction, or urgent target-vessel revascularization within 30 days after the index procedure."[51]

Explanation. Any differences in outcome measures in the new trial compared with trials that established efficacy of the reference treatment should be noted and explained. In particular,

authors should note any differences in the timing of evaluation. Ideally, outcomes should not be changed, but changes may be indicated by improvements in the understanding, management, and prognosis of a disease. For example, early acquired immunodeficiency syndrome (AIDS) trials had death as the primary outcome, but as deaths became uncommon, the focus shifted to AIDS clinical events, then shifted again to surrogate markers as clinical events became uncommon.

Item 7a: Sample Size. *Standard CONSORT item*: How sample size was determined. *Extension for noninferiority trials*: Whether the sample size was calculated using a noninferiority criterion and, if so, what the noninferiority margin was.

Example 1 (noninferiority). "Using data from the nonfatal stroke outcomes from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial and from the meta-analysis by the Antithrombotic Trialists' Collaboration . . . , we derived an estimated odds ratio for clopidogrel being better than placebo for the outcome of nonfatal stroke: 1.377 (95% confidence interval [CI], 1.155 to 1.645). Thus, to ensure that the aspirin plus extended-release dipyridamole preserved at least half the effect of clopidogrel, the noninferiority margin was set at 1.075, an effect size equal to half the lower limit of the confidence interval. . . . With 1715 recurrent strokes, we would have a statistical power of 82% to reject the inferiority null hypothesis, assuming a 6.5% relative risk reduction with aspirin plus extended-release dipyridamole as compared with clopidogrel."[45]

Example 2 (equivalence). "The margin of equivalence, Δ, was 5% and the range −5% to 5% was predefined as an acceptable range of completion rates [of medical abortion] between the two types of providers. The margin was based on clinically and statistically important differences as well as ethical criteria, cost, and feasibility. The sample size of 1086 women was calculated to be sufficient (with a two-sided 95% CI and 80% power) to establish equiva-

lence. The sample size calculation allowed for 10% loss to follow-up. . . . "[52]

Explanation. The margin of noninferiority Δ should be specified and preferably justified on clinical grounds. If Δ is too large, there will be too great a risk of accepting a truly inferior treatment as noninferior. This concern is especially relevant for serious outcomes such as mortality. On the other hand, defining a very small Δ might produce inconclusive results, requiring an extremely large trial if adequate power is to be achieved. If Δ is chosen to be a proportion of the difference between reference treatment and placebo in previous trials (ratio approach),[53] that should be noted.

Calculation of power requires that the investigators stipulate the expected response in each group. It is common for these values to be set equal so that the power of the trial corresponds to the case in which there is a zero difference between the 2 groups. The power can be higher if the new treatment is assumed to be more effective than the reference treatment or lower if it is assumed to be less effective.[54]

Two reviews of published trials found that less than three-quarters of reports of noninferiority and equivalence trials reported a sample-size calculation that incorporated Δ.[24,33]

Item 7b: Interim analyses and stopping guidelines. *Standard CONSORT item*: When applicable, explanation of any interim analyses and stopping guidelines. *Extension for noninferiority trials*: To which outcome(s) they apply and whether related to a noninferiority hypothesis.

Example [noninferiority trial with stopping criterion based on superiority]. "A data and safety monitoring board reviewed the data periodically for safety and efficacy. They could recommend stopping the study if a benefit in favour of oral anticoagulation therapy was shown, such that the hazard ratio for clopidogrel plus aspirin versus oral anticoagulation therapy exceeded 1.0 by more than 3 SD at either of two formal interim analyses, timed to occur when 50% or 75% of events had occurred. . . . "[55]

Explanation. In superiority trials, if an interim analysis shows clear evidence of the efficacy of the new treatment, it may be considered unethical to continue the trial and deny the new effective treatment to the control group. In contrast, in noninferiority trials, if noninferiority is demonstrated for the primary outcome (using the prestated noninferiority margin) before completion of the trial, there is less ethical need to stop the trial because the control group is already receiving the standard treatment and the experimental treatment is not appearing appreciably worse. Also, if noninferiority is evident at interim analysis and the point estimate is favorable, the investigators or the data monitoring committee may then wish to continue in the hope of demonstrating superiority.[38] In noninferiority trials it is therefore often more appropriate to base stopping rules on safety outcomes and superiority hypotheses.[56] Stopping rules for efficacy in noninferiority trials may be asymmetric,[57] ie, may favor stopping early if the new treatment is appearing worse than the standard but continuing longer if the new treatment is appearing better. Formal stopping rules for futility may be particularly important for noninferiority trials (given that the comparison is with a proven standard therapy). It has been suggested that relating the observed effect to the point of "no effect" rather than the noninferiority margin may be more appropriate for considering futility and harm in noninferiority trials and that "the data would have to show convincing evidence of harm before the trial would be stopped for futility."[58]

Item 12a: Statistical Methods. *Standard CONSORT item*: Statistical methods used to compare groups for primary and secondary outcomes. *Extension for noninferiority trials*: Whether a 1- or 2-sided confidence interval approach was used.

Example 1 (noninferiority, continuous outcome). "The primary efficacy endpoint was the mean change in pain intensity. . . . Study endpoints were analysed primarily for the per protocol population

Figure 2. Confidence Intervals and the Noninferiority Margin (Item 17a, Example 1)
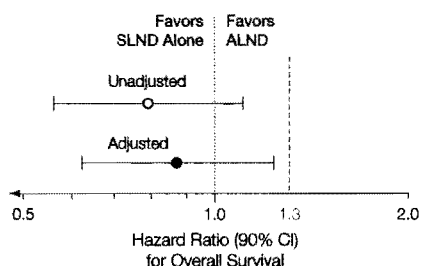
Hazard ratios (HRs) comparing overall survival between the axillary lymph node dissection (ALND) and sentinel lymph node dissection (SLND)–alone groups. Blue dashed line at HR=1.3 indicates noninferiority margin; blue-tinted region to the left of HR=1.3 indicates values for which SLND alone would be considered noninferior to SLND plus ALND. Reproduced from Giuliano et al.[62]

and repeated, for sensitivity reasons, for the intention-to-treat (ITT) population. For most efficacy endpoints, a confidence interval (CI) approach was used on an analysis of covariance (ANCOVA) model, with a two-sided 5% level of significance. . . . For the primary efficacy endpoint, non-inferiority of lumiracoxib to indomethacin could be claimed if the lower limit of the CI [for the difference in mean change of pain intensity assessed on a 5-point Likert scale] was greater than −0.5. This test for non-inferiority was only performed for the primary efficacy variable; all other secondary variables were tests of superiority of lumiracoxib versus indomethacin."[59]

Example 2 (noninferiority, binary outcome). "The trial was powered for separate comparisons between the control group [unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor] and each of the two investigational groups. We used sequential noninferiority and superiority analyses with hierarchical end-point testing, with the type I error controlled by the Benjamini and Hochberg procedure, as previously described. Noninferiority was declared if the upper limit of the one-sided 97.5% confidence interval (CI) for the event rate in the investigational group did not exceed a relative margin of 25% from the event rate in the control group [risk

ratio = 1.25], equivalent to a one-sided test with an alpha value of 0.025. A two-sided alpha value of 0.05 was used for superiority testing."[60]

Example 3 (equivalence, binary outcome). "To assess the equivalence between midlevel healthcare providers and doctors, the risk difference between the two provider types together with their [two-sided] 95% CI was derived by use of a generalised estimating equation (GEE) model . . . [The primary endpoint was complete abortion] . . . If the CI of the risk difference between the two groups falls within the predetermined margin of equivalence (−5% to 5%), the two types of providers can be considered equivalent. . . . The analyses for the primary and secondary endpoints were on an intention-to-treat basis, supplemented by per-protocol analysis of the primary endpoint."[52]

Explanation. Tests of noninferiority need to be related to the Δ and α as prespecified in the noninferiority hypothesis. It should be specified whether an absolute difference between treatments or a relative measure, or both, will be used. Judgment of the results in relation to the study hypothesis is based on the location of the whole CI in relation to Δ (Figure 1). For noninferiority trials, the upper bound of the 2-sided $(1 − 2\alpha)$ × 100% CI for the (deleterious) treatment effect or the upper bound of the 1-sided $(1 − \alpha)$ × 100% CI has to be below the margin Δ to declare that noninferiority has been shown, with a significance level α. The 2-sided CI provides additional information, in particular for the situation in which the new treatment is superior to the reference treatment. For equivalence trials, equivalence is demonstrated if the entire 2-sided $(1 − \alpha)$ × 100% CI lies within $−\Delta$ and Δ.

If noninferiority has been demonstrated, it is then acceptable to assess whether the new treatment appears superior to the reference treatment, using an appropriate test or CI, with a significance level or confidence, respectively, defined a priori in the protocol and with an ITT analysis. Conversely, occasionally a trial protocol may specify that if superiority is not demonstrated, a noninferior-

ity analysis will be performed.[61] Such sequential testing should be fully explained.

Results

Item 17a: Outcomes and Estimation. *Standard CONSORT item:* For each primary and secondary outcome, results for each group, the estimated effect size and its precision (such as 95% CI). *Extension for noninferiority trials:* For the outcome(s) for which noninferiority was hypothesized, a figure showing CIs and the noninferiority margin may be useful.

Example (noninferiority of new treatment). "The unadjusted HR comparing overall survival between the SLND [sentinel lymph node dissection]-alone group and the ALND [axillary lymph node dissection] group was 0.79 (90% CI, 0.56-1.10), which did not cross the specified boundary of 1.3. The HR for overall survival adjusting for adjuvant therapy . . . and age for the SLND-alone group compared with the ALND group was 0.87 (90% CI, 0.62-1.23)" (FIGURE 2).[62]

Explanation. A figure helps readers to interpret the result based on the CI, because it shows graphically where the CI lies with respect to the null value (if a risk difference is used) or to 1 (if a relative measure is used) and with respect to the margin of noninferiority or the margins of equivalence. In the example the new treatment was noninferior. The figure can be used to show graphically the results of different analyses, eg, with or without adjustment (Figure 2) or ITT and per protocol.[63]

Only 1 of 47 published equivalence or noninferiority trials in ophthalmology evaluating prostaglandins depicted the CI graphically with the prespecified noninferiority or equivalence margin.[24]

Discussion

Item 22: Interpretation. *Standard CONSORT item:* Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence. *Extension for noninferiority trials:* Interpret results in relation to the noninferiority hypothesis. If a superi-

ority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, provide justification for switching.

Example 1 (concluding inferiority of new drug or conventional superiority of reference drug). "Although the trial was intended to assess the non-inferiority of tirobifan as compared with abciximab, the findings demonstrated that tirobifan 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)."[51]

Example 2 (concluding noninferiority of new drug from a trial designed to assess superiority). "The SYNERGY protocol prespecified that if enoxaparin was not demonstrated to be superior to unfractionated heparin, a non-inferiority analysis was to be performed. . . . Enaxoparin was not superior to unfractionated heparin but was noninferior for the treatment of high-risk patients with non ST-segment elevation [acute coronary syndromes]."[61]

Example 3 (concluding equivalence). "The risk difference for complete abortion was 1.24% (95% CI −0.53 to 3.02), which falls within the predefined equivalence range (−5% to 5%). . . . The provision of medical abortion up to 9 weeks' gestation by midlevel providers and doctors was similar in . . . effectiveness."[52]

Explanation. The results of any trial must be interpreted in relation to its aims. As shown in Figure 1, assuming an adverse outcome calculated as new vs reference, if the upper bound of the 2-sided $(1 − 2\alpha) \times 100\%$ CI for the difference between treatments is below Δ, noninferiority may be claimed. Alternative explanations such as poor adherence, dropouts, recruitment of patients un-

likely to respond, and treatment crossovers may need to be considered (see "Conduct" in eAppendix). If instead the upper bound is above the noninferiority margin Δ, the null hypothesis of inferiority remains plausible. If the 2-sided CI for the treatment difference is entirely to the left of zero as in case A of Figure 1, then it can be sensibly concluded that there is statistically significant evidence that the new treatment is superior to reference, if the superiority hypothesis is defined a priori in the protocol and the analysis is ITT.

It should be indicated whether the conclusion relating to noninferiority or equivalence is based on ITT or per-protocol analysis or both and whether those conclusions are stable with respect to different types of analyses (eg, ITT, per-protocol). Conclusions should preferably be stated in terms of the pre-specified noninferiority or equivalence margin using language consistent with the aim of the trial (eg, treatment A is "noninferior to" or "equivalent to" treatment B).[32,33,47]

COMMENT

Available efficacious active treatments can make use of placebo controls unethical.[64] Noninferiority trials, comparing a new treatment with a standard, are becoming frequent because of the need to replace standard treatments by other treatments having comparable efficacy but presenting other advantages. Even in cases for which a treatment is efficacious on some measures, eg, depression scales, it may not be efficacious for a rarer but arguably more important outcome, eg, suicide.[65]

It is not our intent to promote noninferiority or equivalence trials but to contribute to better reporting and understanding of these trials: the design of a trial should be appropriate to the question to be answered.[66] Reports of noninferiority and equivalence trials must be clear enough to allow readers to interpret results reliably. Accordingly, we have provided an updated extension to the CONSORT Statement to facilitate appropriate reporting of noninferiority and equivalence trials.

The present recommendations are among a series of extensions to the CONSORT Statement. The current versions of all CONSORT recommendations are available at http://www.consort-statement.org.

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