The ethics of non-inferiority trials

Silvio Garattini and Vittorio Bertele'[1] rightly caution about the traps to be avoided in doing non-inferiority trials, but go too far in suggesting that such trials should be uniformly banned "because they are unethical". A good example of the appropriate use of a non-inferiority trial is the current research programmes to develop new drugs for treatment of drug-sensitive tuberculosis.

Internationally recommended regimens are highly effective, curing 95% or more of patients in clinical trials in a wide variety of settings.[2,3] However, they require a minimum of three drugs which have significant side-effects and need to be given for at least 6 months. Improving on such high cure rates is almost impossible, but shortening treatment duration would improve completion rates and reduce both the time that patients are exposed to potentially toxic drugs and the cost of delivering tuberculosis chemotherapy in the developing world where resources are severely stretched—important medical and public-health goals.

It is impossible to prove that two treatment regimens have the same effect; there will always be some uncertainty surrounding estimates, and a small difference in effect size can never be excluded. However, the risks to patients in a properly done non-inferiority trial are no greater than those in a superiority trial. If non-inferiority designs were banned, there would be no prospect of shortening the duration of chemotherapy for patients with tuberculosis. And that would surely be unethical.

We are part of a consortium that is doing a non-inferiority trial.

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Silvio Garattini and Vittorio Bertele' (Dec 1, p 1875)[1] argue that non-inferiority trials "have no ethical justification, since they do not offer any possible advantage…to patients". Their conclusion is based on the traditional ethic of physicians whereby advocacy for each patient's best interest must supersede all other considerations.[2] However, this ethic only applies to a world where resources for health care are endless and hence do not matter. Yet in a world of limited resources, this ethic can lead to unfair practices, with some patients getting full access to services and others getting none.[2]

Under resource scarcity, non-inferiority trials can therefore be ethical: if the tested treatment is cheaper, savings can be used to treat patients with other diseases who would otherwise be denied treatment. Thus, non-inferiority trials can help to increase population health. Even providing patients with slightly inferior interventions can be ethically justified if savings are substantial and help to treat other patients for a larger benefit.

Finally, it is true that the definition of the inferiority margin is arbitrary, but this certainly also applies to the significance level of α=0·05 in superiority trials.

I declare that I have no conflict of interest.

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In their Viewpoint, Silvio Garattini and Vittorio Bertele'[1] call on the scientific community to ban non-inferiority trials because they are unethical. If efficacy were the only advantage patients might get from clinical trials, I would agree. However, there is no doubt that increasing drug adherence by providing a combination pill, for example, or increasing availability and affordability by providing cheaper drugs would have advantages for current as well as future patients.

Garattini and Bertele' take examples from studies that used non-inferiority designs to argue for their call to ban them. I believe that they confuse non-inferiority as a design with investigators' errors in using it. Setting wide inferiority limits or using statistical rather than clinical difference as a basis for concluding that a drug is non-inferior are investigators' decisions, which are not necessarily right. The appropriate action would be to ban the improper application of the non-inferiority design, not the design itself.

I declare that I have no conflict of interest.

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Silvio Garattini and Vittorio Bertele'[1] assert that "non-inferiority trials are unethical because they disregard patients' interest". This ignores the demonstrable and continuing value of non-inferiority trials. For example, since the introduction of cytotoxic drugs against solid tumours and

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leukaemia, researchers have sought agents with comparable efficacy but less cardiac or renal toxicity.

Similarly, with invasive fungal disease, studies designed to show non-inferiority, have, in fact, shown superiority in response and mortality in prespecified secondary analyses.[2] The studies were clearly in the best interests of patients.

For more on **non-inferiority trials** see *Lancet Infect Dis* 2008; **8:** 209. Published on March 17, 2008

Non-inferiority trials have assessed most modern-day antibiotics, including quinolones, macrolides, β-lactams and, more recently, linezolid, tigecycline, and daptomycin. In clinical practice, equally effective options benefit patients, since physicians can select a therapy on the basis of local resistance, with confidence in the treatment outcome.

With protective therapies (eg, rotavirus vaccine), trialists stipulate that the relative risk of undesirable outcome (eg, intestinal intussusception) should be within acceptable bounds.[3] Because efficacy and safety assessments remain separate, and only considered together when making the final decision, testing for comparability or non-inferiority in one of these dimensions is often inevitable. Are such trials non-inferiority trials or superiority trials?

The collective experience of clinical trialists, regulators, and sponsors continues to embed ethical and scientific rigour into non-inferiority trials.[4,5] We understand that, although superiority trials remain the design of choice, circumstances do not always permit those options.

We strongly support debate on appropriate clinical trial designs, but believe that scientific progress and patients' interests are threatened by Garattini and Bertele's over-reaching conclusions.

We are employees of Pfizer.

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Silvio Garattini and Vittorio Bertele'[1] state that non-inferiority designs are unethical and should be banned because they offer no advantage to present and future patients. Although we appreciate their concerns, we believe the conclusion is fundamentally incorrect and a possible barrier to future clinical research in neglected diseases.

Consider fatal diseases such as sleeping sickness and visceral leishmaniasis. Despite use of existing drugs including melarsoprol or antimonials, the case-fatality rate is still typically 10% (about 8% of patients are not cured and 2% die of drug side-effects). A new drug with the same treatment efficacy, but without iatrogenic case-fatality, would offer a major clinical benefit to current as well as future patients, the latter even more so given increasing patterns of drug resistance.[2]

To prove superiority of a new drug's 92% cure rate over the 90% of the old drugs would require enrolment of 6400 patients (80% power). By contrast, a non-inferiority trial to prove that the new treatment has a cure rate not more than 5% worse than standard therapy requires only 540 patients. Would exposing many more patients to the less safe old drug be more ethical?

An alternative drug regimen with similar efficacy might offer other advantages such as easier administration,[3] lower cost,[4] better tolerability, or, in the case of combination therapy, protection against resistance.[5] Although the advantages of the new treatment might be proven or self-evident—eg, in the case of oral versus intravenous administration—it should still be proven to be sufficiently (not more) efficacious. In the assessment of treatments for neglected tropical diseases, a non-inferiority design is often crucial and ethical.

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Authors' reply

We were interested to read the comments on our provocative paper and are glad it has fuelled the debate. These comments, however, only reflect part of the response: those who disagreed were more motivated to comment publicly than those who sent us endorsements of our position directly.

The question of non-inferiority of cheaper treatments, allowing affordable, wider access with the same resources puzzled us, particularly with regard to treatments for neglected diseases in poor areas.

The assumption of better cost-effectiveness and more health for a wider population implies a superiority hypothesis to be tested by suitable studies, not necessarily randomised controlled ones, but even less so non-inferiority trials.

Andrew Nunn and colleagues note the importance of shortening tuberculosis chemotherapy not only to free resources for wider access but also to reduce the effects of treatment toxicity. This additional objective, aiming at more health for individuals besides that for the population, also implies a superiority hypothesis to be addressed as such. Better safety at the cost of similar or even lower efficacy can be assessed by combined endpoints measuring an adjusted (or weighted) algebraic trade-off of the two items.

This also applies to the comments of Christy Chuang-Stein and colleagues and Elsayed Soliman, who justify the documentation of non-inferior efficacy to take advantage of different toxicological profiles. Joris Menten and Marleen Boelaert find this approach unfeasible in the case they make. However, only an artifact allows a smaller sample size, which means accepting up to 5% more deaths from treatment failure in order to avoid 2% fatalities from drug toxicity. Since there is no demonstrable advantage in terms of overall mortality, the hypothesis should not be tested.

Chuang-Stein and colleagues also indicate the legitimacy of non-inferiority trials to provide non-responsive patients with more options. The efficacy of new antibiotics in non-responders to current drugs provides the appropriate solution to the problem of resistance, while non-inferiority in the overall patient population would fail.

The test of superiority should also be adopted when seeking better tolerability or ease of use, since these should both improve compliance, hence also effectiveness.

New drugs should always aim to provide added value. This cannot be documented by non-inferiority trials which simply present an excuse not to look for differences.

We declare that we have no conflict of interest.

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Now voyager sail thou forth to seek and find

Richard Horton (Jan 5, p 3)[1] is far-sighted about the essential fabric of a scholarship that is "open to new thinking", takes "risks", and requires an "environment of freedom". If, in 2008, the young Hans Sloane (future President of the Royal College of Physicians), Joseph Banks (future President of the Royal Society), or Charles Darwin (future Fellow of the Royal Geographical Society) applied to join a voyage of discovery, what modern bureaucracy would support those young explorers?

Across disciplines and especially during postgraduate training, new academic skills should be cultivated, emancipating medicine "beyond the narrow confines of professional interest"[1] towards "a life changing experience".[2] The Hollow Men behind the new *Research Excellence Framework*[3] seem to understand very little about "higher" education. One of their blind spots is that there is a *community* of scholarship in which both ideas and academic innovators develop over time.[4] If that community is to advance doctors' "purpose in society",[1] it might help to promote new, even risky, collaborations between clinicians and social scientists.[5]

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Survival rates in very preterm babies in England and Wales

We read your Series on preterm birth, especially the paper on mortality and sequelae of preterm birth (Jan 19, p 261),[1] with interest, since statistics on preterm birth and gestation-specific infant mortality have recently become available for the first time for England and Wales as a whole.[2,3,4]

These data relate to all 645 887 live-births that occurred in England and Wales in 2005. They are therefore a valuable addition to the UK data presented in table 1 in the paper by Saroj Saigal and Lex Doyle because they are based on larger numbers of very preterm births and relate to the whole population. They also concern a more

	Gestational age (completed weeks)				
	22	23	24	25	26
Number of livebirths	152	283	474	499	704
Number of deaths under the age of 1 year	144	239	276	176	167
Proportion surviving to the age of 1 year	5·3%	15·6%	41·8%	64·7%	76·3%
Infant deaths per 1000 livebirths	947·4	844·5	582·3	352·7	237·2

Data from Office for National Statistics.[2]

Table: **Deaths in the first year of life among babies born in England and Wales in 2005**