

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.

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.

*Christy Chuang-Stein,
Mohan Beltangady, Michael Dunne,
Briggs Morrison
christy.j.chuang-stein@pfizer.com

Pfizer Global Research and Development,
New London, CT 06320, USA

- 1 Garattini S, Bertele V. Non-inferiority trials are unethical because they disregard patients' interests. *Lancet* 2007; **370**: 1875–77.
- 2 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–15.
- 3 Vesikari T, Matson O, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; **354**: 23–33.
- 4 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: choice of control group and related issues in clinical trials (ICH E10). Geneva: ICH, 2000. <http://www.ich.org/LOB/media/MEDIA486.pdf> (accessed Feb 20, 2008).
- 5 EMEA Committee for Medical Products for Human Use. Guideline on the choice of the non-inferiority margin. London: EMEA, 2005. <http://www.emea.europa.eu/pdfs/human/ewp/215899en.pdf> (accessed Feb 20, 2008).

Silvio Garattini and Vittorio Bertele¹ 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.

We declare that we have no conflict of interest.

*Joris Menten, Marleen Boelaert
jmenten@itg.be

Department of Public Health, Institute for Tropical Medicine, B2000 Antwerp, Belgium

- 1 Garattini S, Bertele V. Non-inferiority trials are unethical because they disregard patients' interests. *Lancet* 2007; **370**: 1875–77.
- 2 Croft SL, Sundar S, Fairlamb AH. Drug resistance in leishmaniasis. *Clin Microbiol Rev* 2006; **19**: 111–26.
- 3 Jha TK, Sundar S, Thakur CP, et al. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; **341**: 1795–800.
- 4 Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356**: 2571–81.
- 5 Priotto G, Kasparian S, Ngouama D, et al. Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45**: 1435–42.

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.