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The Editor
The Lancet
32 Jamestown Road
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Dear Sir,

We greatly enjoyed the polemic of Profs Garattini and Bertele' (Lancet 2007, 370, 1875-77) and share many of their concerns about the technical aspects of non-inferiority trial design and interpretation. We do not, however, share their view that non-inferiority studies are inherently unethical for two fundamental reasons –

- 1 The efficacy of a medicine in a randomised controlled clinical trial (RCT) is a fairly poor guide to both its real world effectiveness and tolerability and its eventual place in therapy. The development of a number of similar medicines allows the prescribing community to establish, in the real world, the 'best of breed' in effectiveness/tolerability terms, which may show no difference in efficacy in an RCT. Randomisation to a new medicine in a non-inferiority study thus brings the possible benefit of receiving the drug with greater effectiveness or tolerability, a benefit possibly as great as receiving the medicine with greater efficacy in a superiority study.
- 2 Real world safety of new medicines is not apparent until they have been in widespread use, often for several years. Having several medicines of similar efficacy (or even effectiveness) in the therapeutic armamentarium is useful when safety concerns arise about an individual medicine, meaning that equivalent alternatives are readily available. The recent examples of rosiglitazone and cerivastatin show the benefits of having more than one agent in a therapeutic class, even if the efficacy is very similar. Randomisation in a non-inferiority study can lead to the benefit of receiving what turns out to be the safer therapy, even if the safety benefit is not immediately apparent.

Given the desirability of several therapeutic options we support the development of medicines which, at first sight, may appear very similar. The possible benefits to study participants of receiving, in a non-inferiority study, a drug which may be more effective, be better tolerated or prove to have a better safety profile is akin to the possible benefit of greater efficacy in a superiority study and provides the clinical equipoise to render such non-inferiority studies ethical. Both investigators and study participants should be fully aware of the nature of the study and be encouraged to consider the implications.

Ultimately all patients are unique individuals and an ethical prescribing decision must look at the needs of the individual, informed but not constrained by data from the rather artificial setting of RCTs.

Yours sincerely

A handwritten signature in black ink, appearing to read 'K. R. Paterson', with a horizontal line underneath the name.

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