Reviewer's report

Title: Through the Looking Glass: Understanding Non-Inferiority

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Reviewer: Anthony Marson

Reviewer's report:

The manuscript is for a review addressing issues around non-inferiority trials, which is well written. The perspective taken is a regulatory one with reference to EMA and FDA regulations. I don't know what brief the authors were given, but in my view it would be helpful to widen the scope to include issues that are relevant to publicly funded / phase 4 trials where the intention is to inform clinical practice and policy rather than regulators. Most of my comments relate to this and are thus discretionary.

1. It would have been helpful if the pages were numbered. Pages 2 and 3 highlight referencing problems. It appears that the software could not find the desired references or figures. This made it more of challenge to read and review.

2. Page 3 2nd para. Is it generally true that less rigour biases towards non-inferiority? Randomisation, blinding and ITT aim to prevent false positive results. I presume that ‘sloppy’ refers to ‘biocreep’ and problems with assay sensitivity. If so this needs better explaining.

3. Page 7. In the sloppy hypothetical trial where treatments are mingled, would the fault here be with the randomisation? Surely the problem would be with implementation of the treatment or policy to which patients were allocated.

4. page 8. Choosing the margin. Should patients not participate in the process of deciding delta? Also, the authors state that this approach may be of limited success in a ‘scientific or regulatory setting’. What about trials that are attempting to inform clinical decisions and policy rather than regulators?

5. There needs to be some discussion around the clinical relevance of 95-95 method and the synthesis method. While there approaches might allow trials that convince the regulators that a treatment has efficacy, large margins defined by this method might not be at all convincing to clinicians and patients that non-inferiority has been demonstrated.

6. The discussion in section 5 highlights a regulatory focus on being able to infer, from a non-inferiority trial, that a new treatment is better than placebo. Clinicians and patients are more interested to know whether a new treatment is ‘non-inferior’ to a standard treatment whereby the results exclude an important difference at the ‘non-inferior end’. This difference in emphasis results in regulatory trials that do little to inform clinical decision making.
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**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests