Author's response to reviews

Title: An investigation of minimisation criteria

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We below give a point by point response to the second reviewer (the outstanding comment from reviewer 1 is covered in point 8):

Minor essential revisions

1. The wording of the abstract has been amended and Senn (2004) is referenced in the text (page 5).

2. The questions posed and parameters to be selected (page 6) have been combined to avoid repetition. Deterministic allocation is considered (results for randomisation weights=1); this point is highlighted on page 12.

3. We have emphasised the usefulness of the technique across a variety of sample sizes. We have included an example with a small sample size of only 40 patients and this is contrasted to the larger sample sizes of 500 generated. The same scenario is simulated with both 40 and 500 patients (figures 2 and 3) showing the extent to which sample size is associated with the success of the minimisation process in equalising the distribution of prognostic factors between treatment groups.

4. A sentence has been added to the discussion (page 21) stating that an independent 3rd party should perform the allocations.

5. We agree that use of the term 'prognostic' rather than 'confounding' may be preferable as it is more in keeping with the rest of the minimisation literature. Futhermore, factors will not be confounding once minimisation has been successfully applied. Hence we have edited the text accordingly.

6. We also agree with the reviewer that 'bias' might be more usefully labelled 'weighted randomisation' and have edited the text accordingly.

7. We have added a reference to Vaughan Reed and Wickham (page 20)

8. In response to the first reviewer also, we have now edited the axis for figure 3 to be the same as those for the other figures.

9. We have added a sentence (page 23) about the potential for trade-off between minimisation and stratification where the number of potential confounders is small.

10. In the discussion (page 19) we state what can be concluded from the simulated studies undertaken. In particular we note that any randomisation weighting has a large effect and increasing the randomisation weight over 5 (p>0.83) has little effect on outcomes.

Discretionary revisions

1. The results show that introducing randomisation weights as small as 2 (p=0.67) has a large effect on the success of the minimisation in ensuring even distribution of prognostic factors between treatment groups. Hence the argument that there is no point minimising if p is not very close to 1 is shown to be wrong.
2. We have removed the word 'clinically' from the justification for the use of the 95th centiles (page 13).

3. The ability of the software to extend to multi-arm trials is mentioned in the discussion (page 23).