

Stratified merged randomisation as an alternative to minimisation: a simulation study

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Introduction

The randomisation method of minimisation aims to ensure balance across key prognostic variables, even in small trials. Simple randomisation will balance groups on average, but in small trials clinically important imbalances are more likely to occur. Minimisation avoids “embarrassing” random chance imbalances that may raise questions when results are presented. Note that balance of prognostic factors is not strictly required for valid statistical inference, but balance via minimisation is likely to increase statistical efficiency [Senn, 2013]. Good Clinical Practice (GCP) states that if minimisation is used, it should contain a random element. This means that the patient is randomised to an alternative group with probability >0 , (e.g. 0.2). A disadvantage of minimisation is that it can be too predictable: especially for unblinded trials.

Stratified Merged Randomisation (SMR)

Stratified merged randomisation (SMR) was developed by Stéphanie van der Pas [Clinical Trials; 2019, 16(3):246-52]. This method involves merging two separate block randomisation lists (called basis allocations). The result is a moderately unpredictable randomisation list, with maximum imbalance only slightly higher than the basis allocations. In particular, SMR is less predictable than block randomisation when the maximum imbalance is equivalent.

Research Questions

1. Could SMR be used as an alternative to minimisation in clinical trials?
2. What random element to use for minimisation?

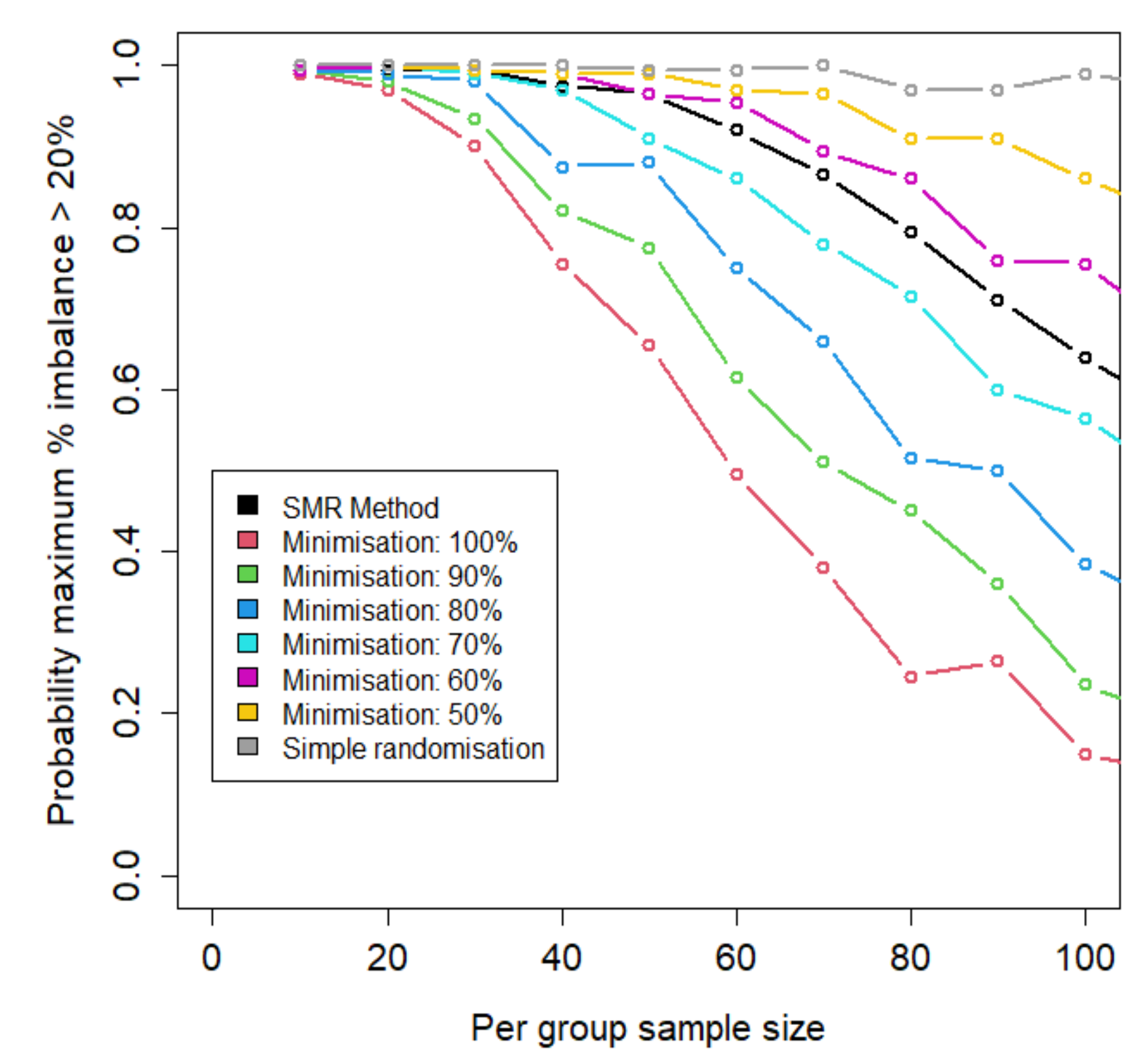
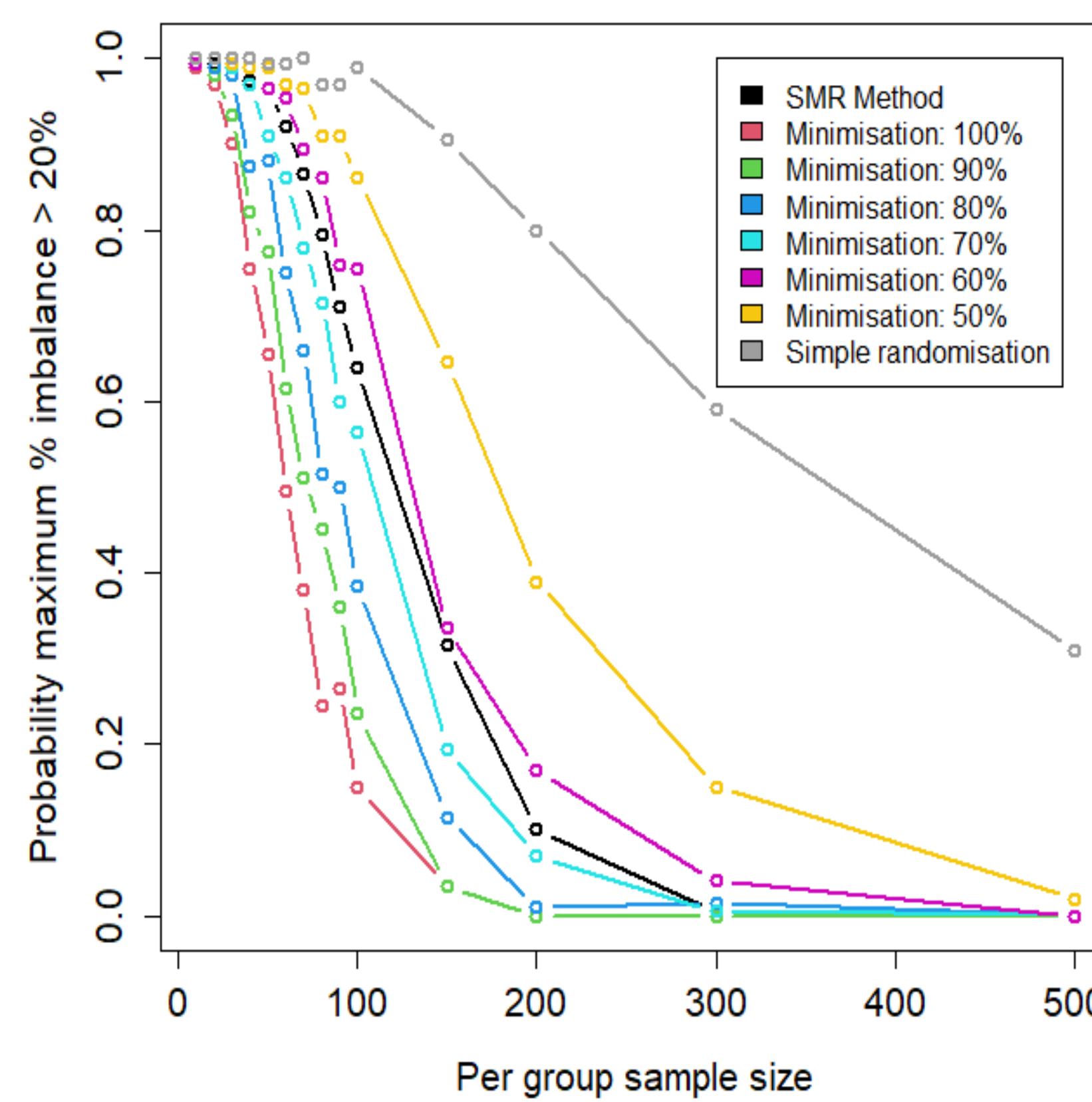
Methods

In the context of 2 and 3-arm trial designs, a simulation method compared SMR, simple randomisation, and minimisation (with random elements of various sizes) in terms of (i) maximum between-arm imbalance, and (ii) unpredictability, based on the correct guess probability [see van der Pas, 2019]. We used the DEFINE trial to inform our simulations, which was a 3-arm early phase trial involving 20 patients per group (60 in total), utilising minimisation with 80% random element and four minimisation factors [Gaughan et al., 2021].

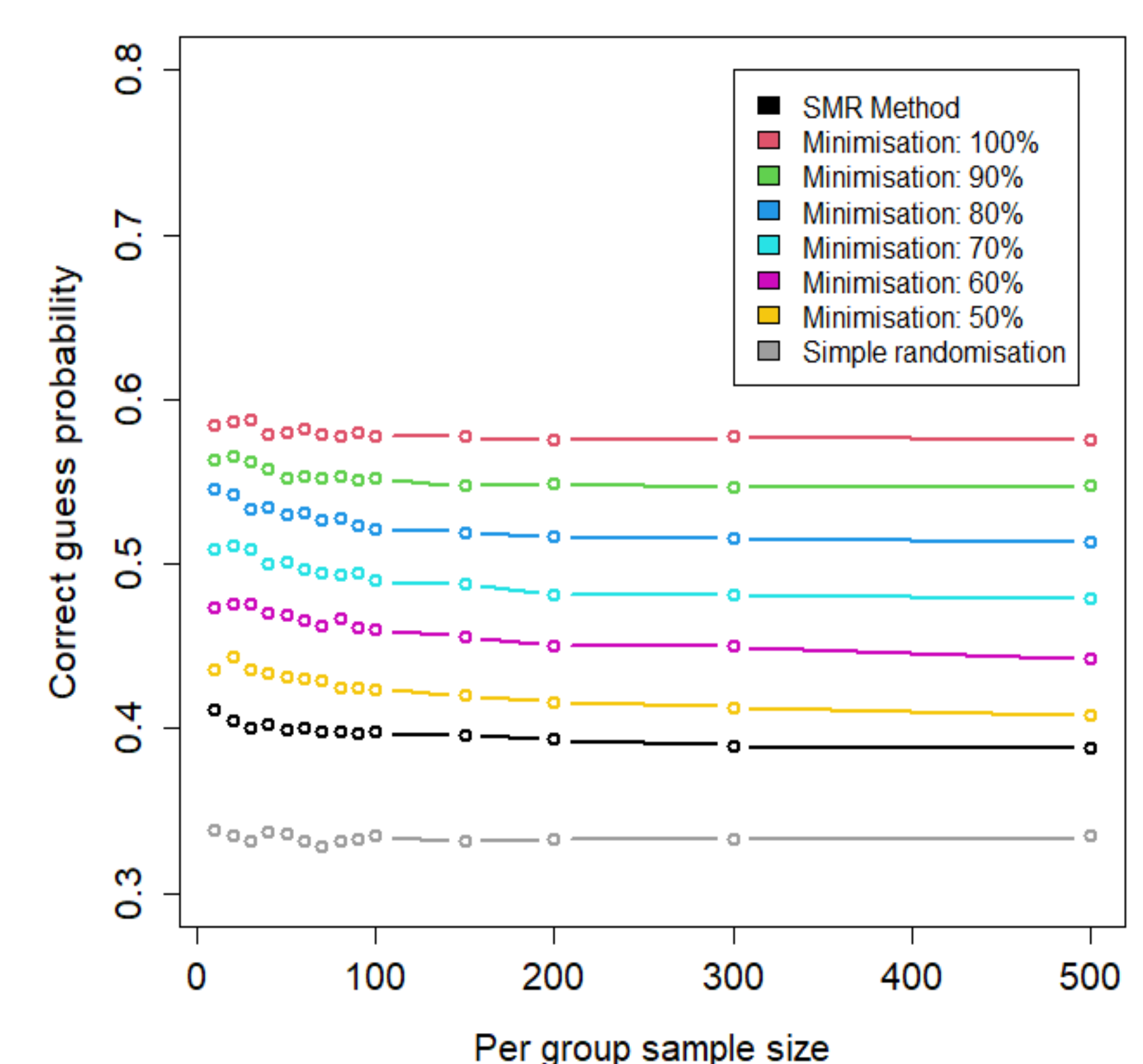
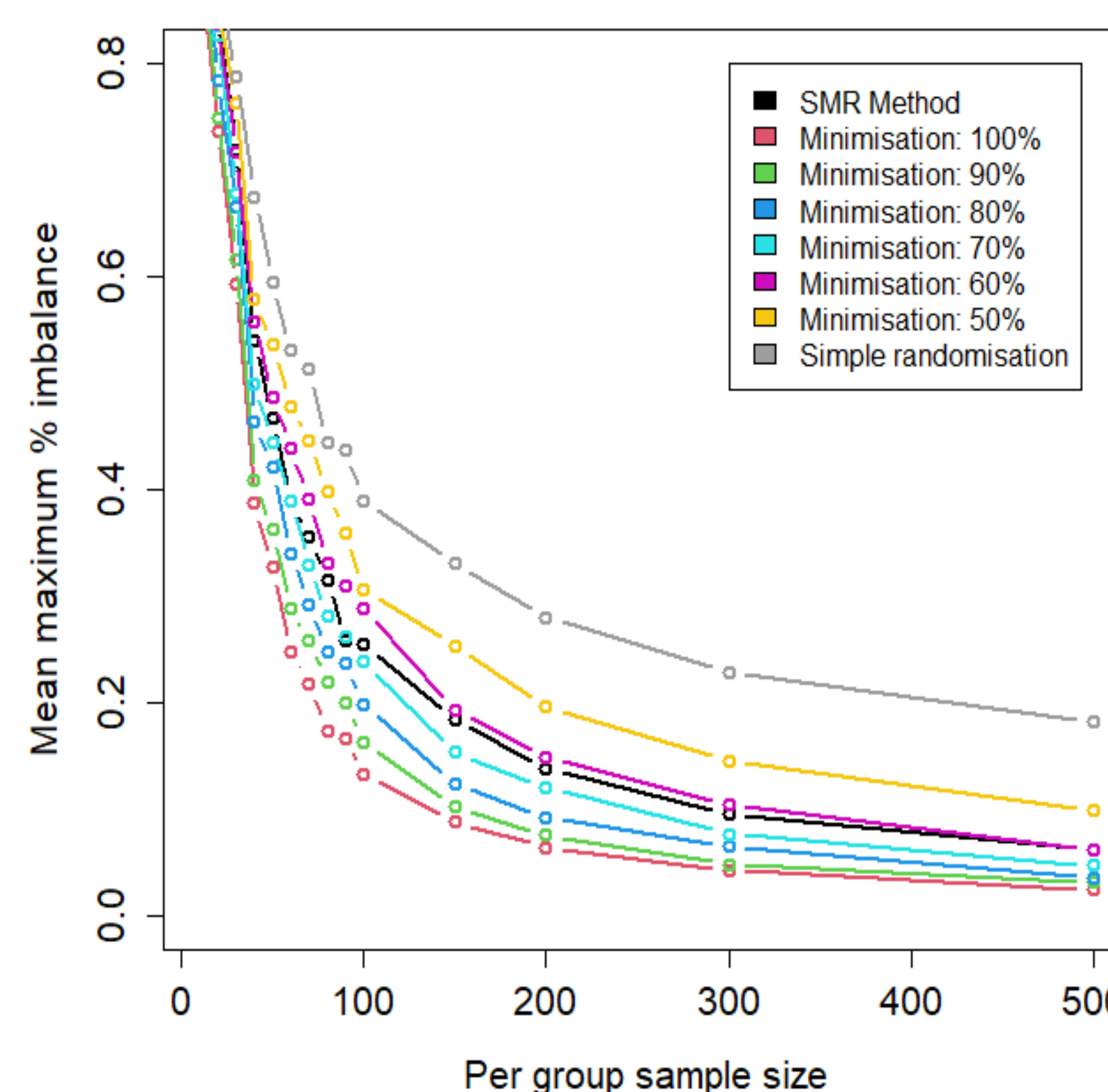
Regarding SMR, an extension of the method was used in simulations to cope with multiple strata. This involved generating a separate merged allocation list for each possible combination of minimisation factors.

Simulation was conducted in R software. Performance of the randomisation methods was assessed after varying per group sample sizes from 10 to 500 and random elements from 50% up to 100%, while keeping the number of factors constant. A total of 200 replicate trials were generated per scenario.

Results



Figures 1 and 2 show the probability of maximum percentage imbalance $>20\%$ across all simulated trials for 10-500 per group and 10-100 per group sample sizes respectively.



Figures 3 and 4 show the mean maximum percentage imbalance and correct guess probabilities respectively for per group samples in the range 10-500.

Results varied slightly depending on (i) the proportions within each of the categories of the minimisation factors, and (ii) the number of trial arms. Figures shown are for the scenario of unequal proportions within each of the minimisation factor categories (e.g. 10% and 90%) in a 3-arm trial. Overall, SMR had similar levels of between-arm balance to using 60% minimisation in three arm trials, and 70% minimisation in two arm trials. However, SMR showed superior unpredictability.

Regarding between-arm balance, differences between SMR methods and/or random elements were most acute for sample sizes of around 80-100 participants per group. Using minimisation with 80-90% random element provides much better balance in small trials of between 40 and 200 per group.

Conclusions

SMR is particularly suitable for small unblinded trials where maintaining unpredictability of the randomisation scheme is important. However, using minimisation with 80-90% random element provides much better balance in small trials, and is particularly recommended in trials where there is genuine blinding of participants and trial staff involved in recruitment. In trials aiming to randomise over 400 per group, simple randomisation is a viable alternative to minimisation or SMR.

Note that I did not consider statistical power in this study: imbalance may not necessarily have an adverse effect on statistical power.