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Commentary on *Assigning Subjects to Groups in a Controlled Trial*

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This article and the accompanying spreadsheets will be very useful additions to the researcher's toolbox. The article details a series of scenarios/study designs for which minimisation is advisable in all cases, even for crossover designs based on order of interventions. This is sound advice and the points are well taken.

I am interested in comparing Will's spreadsheets to existing freeware such as the Minim program. Minim permits up to four groups, different proportions of patients in each group, any number of prognostic factors and categories for each factor (subject to a total of 100 categories for all factors together), and different weights for each prognostic factor if required, so that some factors can be treated as more important to balance for than others. On the issue of weighting, I note that for the scenario in which characteristics for all participants are known before allocation, Will's method assigns primary weighting to one factor and equal importance to secondary factors, whereas for allocating participants as they are recruited equal weighting is assigned to all factors. I am unsure what influence this difference would have on resulting estimates of effects if one wished to weight factors more finely. However, I have never been in possession of sufficient a priori information to decide fine-tuned weighting between multiple prognostic factors, and in practice equal importance is the default assumption, so I doubt there is any practical advantage of Minim in this regard. In any event, Will proposes a neat side-step of this potential problem which allows one to 'double-weight' a variable by including it twice with identical values.

Will's method is an advance on Minim in that it may be applied in situations in which characteristics for all people to be allocated are known in advance, rather than solely for scenarios in which participants are allocated as they are recruited. A further advantage over Minim is the ability to include variables measured on a continuous scale, though the article notes that the influence on outcome is likely to be small.

I was pleased to read that subject characteristics need to be included in the analysis. Other statisticians have also made this often neglected point; for example Senn (2007) stated that "the factors that we considered to be important in the first place and led us to adopt minimization… cannot be regarded as irrelevant. So, for example, if we sought to balance by sex, we must include sex as a factor in the analysis." The benefit of including subject characteristics with minimisation is better precision than that with simple random allocation. This is perhaps one reason why minimisation has been described as the "platinum standard" for trials–that is, better than the gold standard of randomisation (Treasure and MacRae, 1998).

The examples used to illustrate the effect of differences between sample and population means (e.g., Figure 1 and associated text) are instructive. Further, deriving a standardised difference between the sample and population means via the standard error of the active intervention mean is a neat way of anchoring minimum sample size to the default for the minimum important difference (MID) of 0.2 standard deviations. This reveals that the standardised mean difference between a sample mean and the population mean is typically >MID for a group sample size <25.

The alternative analysis method to account for minimisation that Will proposes for the situation is which assignment is performed after all participants have been recruited has echoes of propensity score matching–a method used in observational/controlled before-and-after studies (non-randomised). There is a long-standing debate in the propensity score matching literature on whether the matched samples should be treated as paired or as independent groups. Will proposes the former to increase precision and backs it up with simulations. I need to examine more closely any parallels between Will's method and propensity score matching with respect to this issue. Interestingly, Will notes in

the article that using the pre-post crossover spreadsheet to analyse data from groups minimised on baseline values of the dependent variable produced confidence intervals that were too narrow.

Senn S (2007). A personal view of some controversies in allocating treatment to patients in clinical trials. Statistics in medicine 14, 2661-2674

Treasure T, MacRae KD (1998). Minimisation: the platinum standard for trials? British Medical Journal 317, 362-363

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