Contemporary Clinical Trials 31 (2010) 381–391

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Randomisation in double-blind multicentre trials with many treatments

Malcolm Morrissey, Damian McEntegart *, Martin Lang

Perceptive Informatics, Nottingham UK

ARTICLE INFO

Article history:
Received 21 December 2009
Accepted 2 May 2010

Keywords:
IVR
Latin square
Zelen
'On-demand' allocation
Forced randomisation

ABSTRACT

Trials of many (>2) treatments are common, particularly double-blind dose finding trials in Phase IIb where trials of four or more treatments are often seen. Such trials will almost certainly be conducted at multiple centres given the sponsor's desire to speed up the development program.

When conducting such multicentre trials, the study team will always have to consider the question of whether the randomisation of the trial is to be stratified or balanced in some way by participating centre. In addressing this question there are three considerations: the impact on power, predictability and medication supply requirements.

This paper will describe the use of alternative complex list based randomisation solutions that have been recently developed and implemented; two of the solutions have not previously been presented or published. The techniques maintain various degrees of control over treatment allocations at the centre and study as a whole; consequently the methods help with conserving supplies of medication. Simulation evidence will be presented for each technique.

1. Introduction

It is normal for clinical trials to recruit patients from multiple centres, both to reduce the recruitment time and/or to provide a better basis for the subsequent generalisation of their findings. The ICH E9 statistical guidance [1] notes that multicentre trials "may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame".

Trials of many (>two) treatments are fairly common, particularly double-blind dose finding trials in Phase IIb where trials of five or more treatments are often seen e.g. three doses of the experimental compound, placebo and an active control. Recently attention has focussed on adaptive dose finding trials [2] where there may be a tendency to have more than three doses under investigation e.g. Smith et al. [3] studied seven doses together with placebo and active control groups. Such trials will almost certainly be conducted at multiple centres given the sponsor's desire to speed up the development program.

When conducting multicentre trials, the study team will always have to consider the question of whether the randomisation of the trial is to be stratified or balanced in some way by participating centre. In addressing this question there are three considerations:

a) The impact on study power as a direct effect of the proportions randomised to receive each treatment; the potential disparity in these proportions will largely depend on whether centre stratification is employed. If centre stratification is employed, then there will also be an indirect effect on study power in that the analysis should account for centre. This is to reflect the restriction on the randomisation as outlined in regulatory guidance [4].
b) Any implications for the study blinding. For instance if centre stratification is employed, the blinding might be compromised through emergency code breaking of individual patients (hopefully a rare occurrence) or intelligent guesswork by the investigator (or even the

Abbreviation: IVR, Interactive Voice Response.

* Corresponding author. Statistics & Product Support, Perceptive Informatics, Meadow Grove, Nottingham NG2 3HF, United Kingdom. Tel.: +44 845 3659900; fax: +44 115 9557555.
E-mail address: damian.mcentegart@perceptive.com (D. McEntegart).

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doi:10.1016/j.cct.2010.05.002

study team) through observation of known pharmacological effects. This is not of concern if large block sizes (relative to the number of treatments) are used, but it may be an issue if smaller block sizes are used.

c) The effect on the amount of medication needed to run the study. Ideally this should be a secondary consideration to the two detailed above, but financial and logistical considerations often mean it is important. Regulatory guidance notes that stratification by centre may be done for "practical reasons" [4].

These considerations will generally have different importance in trials with many treatments as compared to trials of two treatments. Generally the more treatments there are, the greater the effect that centre stratification or balancing has on study level balance and on the total amount of study medication needed. Conversely the more treatments there are, the less the likelihood is of potential unblinding due to intelligent guesswork.

In this paper, five different randomisation methods that utilise a permuted blocked listing are investigated. The effects on treatment balance within each method are compared via simulation for an example five treatment arm multicentre clinical trial. A further simulation exercise is also presented, showing the impact on study power. The relative merits for medication stock levels and blinding for each method are discussed.

2. Materials and methods

In this paper we will assume that randomisation is being performed electronically by an Interactive Voice Response (IVR) system, or the web, as will often be the case [5]. For simplicity we will assume that a single pack is being dispensed at the randomisation visit, although the conclusions will apply to the more usual case where further packs are supplied at post-randomisation visits.

To conserve supplies it is usual in such trials to have separate lists for randomisation and supplies with the link being made within the IVR system; thus the appropriate treatment for dispensing is determined from the randomisation list and then a pack of the appropriate type is selected at random from the inventory at the centre [5–7]. Thus any pack can be used for any patient; this potentially offers substantial medication savings compared to using specific patient numbered packs which is the typical method used in non-IVR trials [5]. In the remainder of this paper the supplies list will be referred to as the packaging list. Inventories at centre can be automatically controlled by the IVR system assessing the centres' needs on a regular basis and arranging resupply consignments via automated links with the supply depots.

We will outline the randomisation options facing the study team and discuss the relative merits of each with simulation evidence. The pseudo-study design that will be simulated in all cases has the following characteristics: 240 subjects are randomised across 5 treatment arms in 1:1:1:1:1 ratio, with 60 centres and random recruitment across all centres. For each randomisation method described below, the results of 1000 simulations are considered and compared. Simulation programs for each design were written and performed using the SAS® system [8].

The five randomisation methods investigated are described in the following sections.

2.1. Scheme 1: central unstratified randomisation

Central automated randomisation from a single unstratified list is generally performed in studies where the average number of subjects recruited per centre is expected to be low. This is especially the case in trials with many treatments because if the randomisation is stratified by centre, then there is scope for study level imbalance due to incomplete blocks.

One advantage of the central unstratified randomisation approach is that allocations are completely unpredictable by individual investigators. One potential disadvantage is a slight loss in power if centre is genuinely a prognostic factor, although this will depend on the actual trial; the regulatory requirement to include centre as a factor in the analysis, if it is accounted for in the randomisation, can actually cause a loss of power if the recruitment in some or all centres is low [9,10]. Another disadvantage is the extra medication required, especially in the face of uncertainty about which centres will be the higher recruiters. Supply strategies have to be set that can cope with chance runs on the same treatment being assigned. This is because each allocation is essentially independent of previous allocations at the centre (assuming random recruitment and many centres).

If there is a run on a given treatment at a centre that causes the centre's stock of the associated packs to fall to a low level, or even become unavailable, then the automated supply system must raise a resupply. However, if before the resupply arrives, a new patient presents who should have been randomised to a treatment for which there is currently no appropriate stock, the randomisation has to be either halted or forced to randomly select from the subset of stocks that is available. Which is the preferred alternative is not the topic of this paper and so readers are referred to McEntegart [11]. We merely note that the situation is undesirable and in the ideal world the sponsor would have set the resupply 'trigger' levels for the stocks of each treatment at each centre to avoid such stock-outs. Clearly this comes at a cost of increased supplies wastage at the end of the trial.

2.2. Scheme 2: centre stratified with conventional blocks and blocks balanced across centres

An alternative to central unstratifed randomisation is to stratify the randomisation list by centre. In passing we note that this can be achieved without an electronic system by sending supplies with pack sequence numbers that match the ordering of the sequence numbers in the randomisation blocks that have been allocated to the centre. If the patients are allocated packs in ascending sequence order, then the dispensing will match the randomisation. The simplest way of achieving this is to have patient identification numbers printed on the supply packs. But in what follows below, we continue with our assumption that an IVR system is being used for randomisation.

The advantage of a centre stratified design is that we allocate specific treatment codes to particular centres from the randomisation list. The knowledge of which treatments are to be assigned to the next few patients can be utilised by the