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Sequential balancing: A simple method for treatment allocation in clinical trials

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Abstract

Although minimisation methods have frequently been advocated for treatment allocation in clinical trials, they are not widely used. As this may partly be due to the complexity of the methods, we devised a new and simple minimisation method to balance for prognostic factors, called sequential balancing. Each factor is dealt with sequentially and when a new subject enters the trial, he or she is allocated the treatment that leads to improved balance of the first factor over the treatments. If the balance of the first factor was already satisfactory, then the treatment is allocated that leads to improved balance of the second factor and so on. The algorithm requires no calculations.

We simulated a realistic trial and compared the performance of this method to the performance of alternative allocation strategies: the variance minimisation method, simple randomisation and stratification.

The sequential balancing method led to better balance than randomisation and stratification. In the case of four factors or less, the performance of the sequential balancing method and the variance minimisation method were comparable and the sequence of the factors was not very relevant. When more factors were introduced, the balance of the sequential method remained comparable with the balance achieved with the variance minimisation method for the first four factors, but it started to decrease from the fifth factor onwards.

We conclude that the ease and simplicity of the new method make it an attractive option when balance is required for four factors or less. If there are more than four factors, the sequential balancing method may still be an acceptable option, but the advantage of simplicity has to be weighed against the loss of performance compared to other minimisation methods.

Keywords: Clinical trial; Randomisation; Minimisation; Balance; Subject allocation

1. Introduction

In a clinical trial, it is desirable that important (potential) prognostic factors are balanced over the treatment arms. This not only improves accuracy and precision but also increases the credibility and acceptance of the results [1,2]. On average, randomisation will produce balanced groups, but occasionally serious imbalances may occur, especially in small trials or in trials with many prognostic factors [2,3].

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Stratified randomisation offers protection against imbalance, but only a limited number of factors can be included because stratification aims to achieve balance for each combination of the prognostic factors (stratum). Thus, the number of strata grows exponentially as the number of factors increases.

Minimisation aims to achieve balance for each prognostic factor separately and not for combinations of factors. Consequently, it can cope with more prognostic factors or strata. Minimisation was originally introduced by Taves [4] and Pocock and Simon [5]. In the course of time, many variations have been developed. An excellent overview was published by Scott et al. [6].

Despite the fact that minimisation has been recommended by many authors, it is seldom used [6–9]. This may be because the minimisation methods are fairly complex, which sometimes makes them impractical. For multi-centre trials, for example, a central treatment allocation facility is required that must be contacted for each allocation. Minimisation methods also require programming or calculations need to be done by hand for every subject allocation. This poses a barrier if investigators do not have statistical support or sufficient expertise in programming [6,10]. In the past, trials with poor balance have occurred due to errors in the software algorithms [6,11]. Also, the algorithms are generally difficult to understand and do not seem 'natural' to investigators with little statistical knowledge. The literature shows that minimisation methods do not seem to appeal to clinical investigators, which may cause hesitance towards using them. However, the availability of a method that balances for each prognostic factor in consecutive order, is 'clinically sound', is easy to perform and does not require any calculations can be expected to increase the use of minimisation in clinical trials. We have devised such a minimisation method, called sequential balancing.

2. Sequential balancing

Suppose that in a trial, $v_1, v_2, \ldots v_k$ are factors with potential prognostic value, for example gender, age, severity of the disease and so on. Each factor is divided into classes, e.g. men vs women for gender and young vs middle vs old for age. Each subject belongs to exactly one class for each factor.

Sequential balancing aims to achieve an equal number of subjects on each treatment in each class by considering all the factors in consecutive order: first, try to achieve balance on the first factor; then, when that is successful, try to achieve balance on the second factor, and so on.

In detail, the algorithm allocates the next subject who enters the trial as follows:

Step 1. If for the first factor, v_1, there is a difference of more than one between the number of subjects in the class who are on each treatment, allocate the treatment that reduces the difference. If the difference is one or less, go to step 2.

Step 2. If for the second factor, v2, there is a difference of more than one between the number of subjects in the class who are on each treatment, allocate the treatment that reduces the difference. If the difference is one or less, go to step 3.

The last step in the algorithm is:

Step $k+1$. Allocate a treatment at random.

3. Example: the subclinical hyperthyroidism trial

Subclinical hyperthyroidism is defined as a reduced serum thyrotrophin (TSH) level in the presence of normal free thyroxine (T4) and tri-iodothyronine (T3) levels. The reduced TSH may be caused by overproduction of T4 and/or T3 (endogenous subclinical hyperthyroidism) or thyroid hormone medication. Evidence is accumulating that subclinical hyperthyroidism has important long-term adverse effects, especially increased risks of atrial fibrillation and osteoporosis [12]. As it is controversial whether endogenous subclinical hyperthyroidism should be treated [13], we started a clinical trial that compares treatment with radioactive iodine (I^{131}) to no treatment. The primary outcome parameters are atrial fibrillation and bone mineral density. An estimated 200 patients and a follow-up of 5 years are needed to show a threefold reduction in the incidence of atrial fibrillation, i.e. from approximately 20% to approximately 7% (one-sided test at $P=0.05$, power 80%). It was anticipated that there would only be a small number of patients with endogenous subclinical hyperthyroidism suitable for inclusion in the trial at each centre. Therefore, a total of 40 centres were invited to take part in the trial.