Validation of Adaptive Randomisation Schemes by Re-randomisation in Clinical Trials

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Background

In the design and conduct of randomised clinical trials ensuring that allocation to treatment groups is well balanced among the between the planned treatments is a desirable feature. This has to be achieved without comprising the design aspects of the study. Additionally, if there are important strata in the study design, achieving a treatment balance within the strata will lead to efficient treatment comparisons[1]. In many clinical trials, there is a limited window of opportunity to evaluate important questions, and the ability to repeat a randomised study may be severely limited and so maximum efficiency is essential at the design stage of the trial. This is a key component next to design issues such as trial sample size and outcome assessment/measurement.

Simple randomisation schemes (i.e., coin tossing) whilst ensuring that the estimates of treatment effect are consistent, may, nevertheless result in a trial where there is a large imbalance between the treatment groups and even larger treatment imbalances in key prognostic factors. This may limit both the interpretation of the results of studies and the consequent clinical decisions. In order to address these issues, we have seen the emergence of a number of schemes which attempt to deliver some degree of balance across the treatment allocations whilst at the same time, still providing some degree of randomness. Over and above simple randomisation, two broad randomisation strategies over have gained popularity in clinical trials methodology, namely stratified permuted blocks[3-5] and minimisation[3-8].

Permuted Blocks and Minimisation

The idea behind permuted blocks of size b is to guarantee a treatment allocation balance after b, 2b, 3b … subjects have been randomised. For example, suppose two treatments are being compared A and B. Then, if we wish to maintain a treatment balance after say every b=4 treatment allocations (i.e. permuted blocks of size four), we first form a list of all the possible combinations. In this case, there are six combinations viz., AABB, BBAA, ABAB, BABA, ABBA and BAAB. A block is selected at random and the order given in this block will determine the sequence of the next four treatment allocations. So, if the third block is selected then the order next four treatments to be allocated are A, B, A, B. More complex schemes can be devised (e.g., combining blocks of size 6 and 4) to

minimise the ability of investigators from predicting the next treatment to be allocated (minimising subject selection bias). Provided the number of strata (prognostic factors which impact on the outcome of interest) and/or strata levels is modest, the scheme can be easily adapted to maintain balance of treatment allocation in levels within these strata. In many large multi-centre/multinational clinical trials however, institution is a strata and each hospital will form a level of this strata. Studies recruiting over 100 sites and having say, four other key strata (each with two levels), will require a minimum of 1600 blocking schemes. If sites cease recruiting into a study, blocking schemes may result in a potentially large overall treatment imbalance[6]. Attaining treatment balance within important prognostic factors increases the efficiency of treatment estimates[1].

Minimisation attempts to minimise treatment imbalance marginally across the specified strata. In a two treatment trial for instance, the strata profile for each subject is ascertained (e.g., male under sixty years of age with no previous smoking history in the hospital site 3), the number of previously allocated treatment A's and B's to this profile ascertained (i.e. the sum of each treatment allocation of all subjects fitting this profile) and the absolute value of the difference between these sums calculated. If this difference is zero, the next treatment is allocated a random otherwise the treatment with the smaller sum will be prescribed[3]. This randomisation strategy has proven very popular in clinical trial conduct. Adaptations of this approach (to increase the level of randomness) have also been proposed[7-8] where if, for a particular subject profile the treatment sums are within a specified interval, say $\pm\delta$, then a biased coin is tossed to determine the next treatment allocation. The bias of the coin may vary depending on how close the imbalance (i.e. difference in the treatment sums) is to zero.

Validation Issues

Randomisation and regulation

With guidelines from regulatory authorities stating that dynamic methods "remain highly controversial" and are "strongly discouraged"[9] we face the dilemma of ascertaining the validity of the minimisation randomisation scheme in study for which we wish to achieve good marginal balance among the various prognostic strata levels. It is interesting to note that stratified permuted blocks, which force a treatment allocation 33% of the time are accepted by the regulatory authorities as being legitime randomisation methods.

Suppose then that a trial using minimisation as it randomisation method has been completed and the appropriate outcome for each subject measured. This outcome can be continuous, binary, time to event or ordinal. Assume also that a appropriate statistical test is available to measure the effect of the comparisons of interest.

To fix ideas let us use an example to illustrate the approach. Suppose we are using minimisation to allocate patients to one of two chemotherapy regimens for cervix cancer. Furthermore, the outcome of interest is time to disease progression (PFS) which will be compared using the logrank test and 630 patients have been randomised.

The following re-randomisation strategy has been accepted by the regulatory authorities as being a validation of the randomisation method use (in this case minimisation) as can be described as follows:

Assume that a specific test statistic, the logrank χ^2 is available to test the null hypothesis of no treatment effect in PFS between the two regimens.
The strategy is to perform many simulations of the study and conduct a permutation type test to ascertain how close the nominal significance level (from the study) is to the desired significance level (from the simulations).

Set N, the number of simulations (e.g. N=10000)

Generate N simulated trials as follows:
For trial i, i = 1;;N;

a) For each subject j in the study (j = 1;;630), re-randomise their treatment allocation according to the minimisation algorithm, using a new "seed" as a starting point. Use the previous cumulative strata profile to determine whether the treatment allocation is forced or random. [Random allocations are likely to be different as the random number seed has been changed from the original study. This will produce a new set of treatment assignments for the 630 in the original study]

b) Append the sequence of new treatment assignments to the subjects in the study to their actual outcome data

c) Compute the corresponding statistic for trial i, ($\chi^2_{i.}$) of the difference between the treatments for the outcomes of interest in the re-randomised trial (proportions, time-to-event etc.)

Under the null hypothesis of no difference between the treatment groups, the set $\chi^2_{1,...,}$ χ^2_N represents the distribution of the test statistic using a minimisation randomisation scheme. This procedure is essentially the analogue of a Fisher re-randomisation test preserving the allocation rule and the order of subject entry into the study[10, 11]. Under the null hypothesis, a permutation-test p-value can be obtained by computing the proportion of times, *p* the simulated test-statistic is greater than or equal to the observed one.

A 95% CI for this proportion can be calculated using the results for a binomial proportion. In addition, the asymptotic distribution of the test can be compared to that from the permutation test. This computing the 95% confidence interval based on *p* (i.e. $p \pm 1.96^* \sqrt{[p(1- p)/N]}$ and examining whether this interval contains the nominal p-value (say 5%). If this interval contains the nominal p-value then the minimisation scheme used is a valid randomisation method an that the asymptotic analysis is consistent with that from the permutation test.

Discussion

Alternative approaches of computing the permutation test could also be considered: i) randomly shuffle the patients first and then proceed as above; this procedure essentially assumes that the patients themselves arrived at random which may be questionable, ii) compute a permutation test based on a restricted set of permutations obtained by shuffling only patients who are accrued within a certain period of time. This approach has similar concerns but may be less stringent as we would have to assume that within that window patients still arrive at random. Moreover, using these techniques as a validation tool may be potentially misleading as randomness may be artificially mask a procedure that is strictly deterministic. For example if the randomisation procedure was to allocate treatment A the first 50% of patients, which are recruited into a study and treatment B to the second 50%, then clearly, this procedure, is entirely deterministic. However a validation process by randomly shuffling the patient order would lead to a conclusion that the algorithm satisfactorily generates random allocation sequences.

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