Centralized Treatment Allocation

in Comparative Clinical Trials

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Centralized treatment allocation can help prevent statistical biases and treatment imbalances in multicenter clinical trials.

The past 50 years have brought a tremendous increase in the number of trials using randomization to provide comparability of treatment groups with respect to all known and unknown prognostic factors.[1] Parallel to the increased reliance on randomization to support claims of efficacy and safety of new treatments, active research has sought to identify alternative methods for allocating treatments to subjects in comparative clinical trials. The concept of allocating treatments to subjects using a chance procedure was first introduced by R.A. Fisher in his famous work on experimental design in the 1920s and implemented in medical trials by A.B. Hill in the 1940s.[1]

Pure randomization—that is, choosing the treatment at random every time a new subject enters the study—is only one way in which subjects can be allocated to treatment groups. Other methods have been proposed to

- ensure complete unpredictability of the treatment allocations to prevent selection bias from taking place.
- achieve a good balance between the different treatment groups with respect to important prognostic factors to prevent accidental bias from taking place.
- be simple and foolproof.

Some other objectives (such as maximizing the efficiency of the treatment comparisons when nonlinear models are used in the analysis) have also been contemplated, but they are less important and fall beyond the scope of this article.[2] The three main objectives outlined above are to some extent conflicting, and no method of treatment allocation performs uniformly better for all of them.

Constraints in time, resources, and the availability of clinical trial materials may also influence the selection of a treatment allocation method.[3] Centralized randomization, however, can easily accommodate all the methods discussed here.

Pure randomization, accidental bias

Pure randomization consists of choosing the treatment at random regardless of the subject characteristics. Assuming the trial has two treatment groups (one called *control* and the other *experimental*), pure randomization is equivalent to tossing a coin for every new subject and allocating that subject to control if the coin falls tails and experimental if the coin falls heads. Besides simplicity, the advantage of pure randomization is that its outcome is completely unpredictable; therefore, no selection bias can take place.

The disadvantage of simple randomization is that chance imbalances may occur between the different treatments with respect to subject characteristics. The likelihood of chance imbalances is very low when the number of subjects is large enough—say, several thousand subjects—but the likelihood of imbalances is greater in trials of small or moderate size.

Consider a trial of 100 subjects, half of whom are allocated to control and half to experimental. Suppose further that half of the subjects accrued to the trial are male and half are female. In a perfectly balanced trial, one would expect exactly half of the male subjects and half of the female subjects to be allocated to each treatment group. As it turns out, the chance that such a perfect balance will be achieved with pure randomization is only 11%. There is an 80% chance, however, that the proportion of male subjects will lie between 40% and 60% within each treatment group—and likewise, of course, for female subjects. In other words, there is a 20% chance (1 in 5) that distribution by sex will be more imbalanced than 40:60

Randomization Glossary

accidental bias Bias introduced when more subjects with good prognostic characteristics are allocated to receive one of the treatments, so that this treatment is favored in any treatment comparison.

control group The group of subjects in a controlled study that receives no treatment, a standard treatment, or a placebo.

experimental group The group of subjects in a controlled study that receives the investigational product.

minimization Biasing the treatment allocation so as to achieve treatment balance simultaneously on several subject characteristics and to minimize the total imbalance between the treatment groups.

permuted blocks Sequences of random treatment allocations that contain equal numbers of control and experimental allocations.

selection bias Bias introduced when an investigator can predict the next treatment allocation and select the subject accordingly.

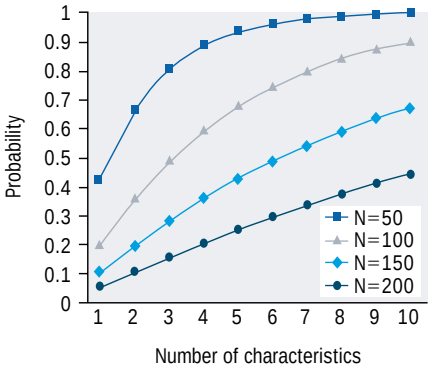

Figure 1. Probability of a "severe" imbalance for at least one subject characteristic (vertical axis), for sample sizes (N) ranging from 50 to 200 and increasing numbers of characteristics.

between the two treatment groups, an imbalance that might be considered severe. If several subject characteristics are considered in addition to sex, the chance of such an imbalance occurring for at least one of the characteristics increases dramatically. With five characteristics, it is up to 68% (2 in 3); with 10 characteristics, it is up to 90% (9 in 10)! Thus, small or medium-sized trials that use pure randomization to allocate treatments to subjects have an unacceptably high chance of a severe imbalance for at least one of the subject characteristics.

Figure 1 shows the probability of severe imbalances for various sample sizes and various numbers of subject characteristics. Clearly, the problem becomes more acute as the sample size decreases and the number of subject characteristics of interest increases.

Why should imbalances in some subject characteristics be a cause for concern? The reason is that if such an imbalance occurred for a characteristic of prognostic importance (such as the subject's condition or the severity of the disease), the imbalance would confound the treatment comparison and create an accidental bias. Such a bias may not be negligible, because the prognostic impact of subject characteristics is often far more important than the effect of therapy. The (unadjusted) statistical test for the treatment comparison remains valid in the presence of accidental bias, but its statistical power may be compromised and the results of the trial may be less convincing if there is a large imbalance in some important prognostic factor(s). Adjusted statistical tests may be performed to account for the imbalanced prognostic factor(s), but unless such tests were prespecified, their data-derived nature will appear suspicious and may cast doubt on the results. It may therefore be desirable to avoid imbalances for important prognostic factors—rather than try to adjust for them—by using treatment allocation methods other than pure randomization.

Stratification, permuted blocks, minimization

Treatment allocation is said to be stratified if it depends on certain subject characteristics called stratification factors (for example, age, sex, disease stage). Stratification factors are usually chosen from among the subject characteristics that are known to have a major impact on the outcome of interest.

In multicenter trials, it is also useful to stratify the treatment allocation by center. There are several reasons for doing so. Subject recruitment patterns may differ substantially between centers, and it may be useful to account for these differences by treating center as a stratification factor. Also, it is sometimes necessary to exclude from a clinical trial all subjects entered by a delinquent center—for example, one from which no follow-up information can be obtained. And participating investigators usually like to view the clinical trial within their own center as if it were a single-center trial.

Permuted blocks. One popular method for implementing a stratified treatment allocation is to use permuted blocks that guarantee perfect balance between the treatment groups after entry of a certain number of subjects. Consider a trial with two treatment groups—control and experimental—and suppose that we wish to take center and sex into account when allocating treatment. We could do this by using permuted blocks for each stratum corresponding to a specific center and sex. Permuted blocks are random sequences of treatment allocations that contain equal numbers of control and experimental allocations. For instance, permuted blocks of four contain two control and two experimental allocations. Within a block, the sequence of treatment allocations is chosen at random from all possible permutations. In our example, all possible permutations are CCEE, CECE, CEEC, ECCE, ECEC, and EECC (C refers to control and E to experimental). The treatment allocation procedure consists of preparing lists of permuted blocks for each combination of center and sex, and reading off the next treatment allocation from that list, as illustrated in Figure 2. Permuted blocks are a static method because the allocation of treatment to a specific subject is predefined in these lists.

The advantage of permuted blocks is that they force periodic balance in the number of subjects allocated to each treatment group within every stratum. One disadvantage is that the last treatment allocation(s) in a block is (are) predictable. In our example, if the first two subjects of a block have been allocated to control, then the next two subjects who enter the trial in that stratum will, with certainty, be allocated to experimental. Although such foreknowledge of the next treatment allocation is not much of an issue in double-blind trials, it can cause selection bias in open-label trials. If some investigators knew that their next subject was going to receive the experimental treatment, for instance, they might select the subject accordingly (for example, a subject with more advanced disease in whom—they hope—the benefit from experimental treatment might be greater).

Another limitation of permuted blocks

Center	Sex	Lists of permuted blocks			
01	Male	~~C~~ ~~E~~ ~~C~~ ~~E~~	E C C E	E C E C	E E C C
01	Female	~~C~~ ~~C~~ ~~E~~ ~~E~~	C E E C	C E C E	E E C C
02	Male	~~C~~ ~~E~~ ~~C~~ ~~E~~	E C E C	E E C C	C E E C
→ 02	Female	~~C~~ ~~E~~ ~~E~~ ~~C~~	E ~~C~~ [E] C	C C E E	C C E E
03	Male	~~E~~ ~~C~~ ~~C~~ ~~E~~	~~C~~ ~~E~~ ~~C~~ ~~E~~	~~C~~ ~~E~~ ~~E~~ C	E C E C
03	Female	~~C~~ ~~C~~ ~~E~~ ~~E~~	~~C~~ ~~E~~ ~~E~~ C	E C C E	C E C E

Figure 2. Stratified treatment allocation using permuted blocks. C refers to control, E to experimental. Treatment allocations already used up are struck through. The next female subject entering the trial in Center 02 will be allocated to experimental.

EXAMPLE of Minimization[a]

	Control	Experimental	Imbalance
Center 02	4	5	1
Female	7	9	2
Total	11	14	3

[a]*The next female subject entering the trial in Center 02 is allocated to control, since that allocation minimizes the total imbalance between control and experimental.*

is that the number of stratification factors must be small (two or three at most). Otherwise, many strata may have fewer subjects than the block size, and a good balance can no longer be guaranteed for all of them.[4]

Minimization is a method that attempts to achieve treatment balance on several subject characteristics simultaneously—not within separate strata.[5] Consider the example above. The next subject to enter the trial is a woman in Center 02. Suppose that at the time this subject enters the trial, the numbers of subjects already allocated to each treatment group are as in the Example of Minimization box.

Minimization consists of biasing the treatment allocation so as to minimize the total imbalance between the treatment groups on some scale.[6] In the implementation shown in the example, this is done by favoring the treatment that has the smallest column total. (This total is not a number of subjects, because some subjects may be counted twice.) In our example, 4 of the 9 subjects already entered in Center 02 have been allocated to control and 5 to experimental, whereas 7 of the 16 women already enrolled have been allocated to control and 9 to experimental. The next female patient in Center 02 should be allocated to control, because 11 is less than 14 (the "total imbalance" is 3 in favor of the experimental group). Hence the treatment allocation will be biased in favor of control—for example, by allocating control with 75% probability and treatment with 25% probability. Had the column totals been equal for both treatments, then either would have been chosen with 50% probability.

The major advantage of using minimization is that treatment balance can be achieved simultaneously for a large number of subject characteristics. Another advantage is that in multicenter trials, treatment allocations are unpredictable in any given center. Minimization is, however, criticized by some statisticians. A primary criticism concerns deterministic implementations of minimization, in which the treatment that minimizes imbalance is given with certainty (rather than with higher probability as in the example above). Such a deterministic algorithm does not guarantee the randomness assumed by the statistical tests used to analyze the trial results. This problem is more theoretical than real in multicenter trials, where the order of entry of the subjects in the various centers and in the various prognostic groups, for all practical purposes, may be assumed to be random. It is, therefore, difficult to conceive how a systematic bias might result from deterministic minimization. Nonetheless, it is just as easy to add the desired randomness in the algorithm by allocating the treatment that minimizes total imbalance with higher probability rather than with certainty.

It is also sometimes claimed that if minimization is used as the method of treatment allocation, the analysis must use permutation tests, rather than the asymptotic tests that can be used with pure randomization. Strictly speaking, this view is well founded, but simulations show that it does not make any material difference what type of test is used. Consequently, minimization can be viewed merely as a convenient way of avoiding accidental bias. It has also been shown that the treatment allocation method has little if any effect on the size and power of the tests used to analyze the results of the trial.[7]

Minimization has been used extensively in clinical trials for a long time. Several European collaborative oncology groups started using it in the early 1980s.[8] The largest trials ever performed in cardiovascular disease used a technique of minimization.[9] The pharmaceutical sector has also used minimization—particularly for trials in which many subject characteristics were known to have a substantial prognostic impact on the outcome of interest.[10]

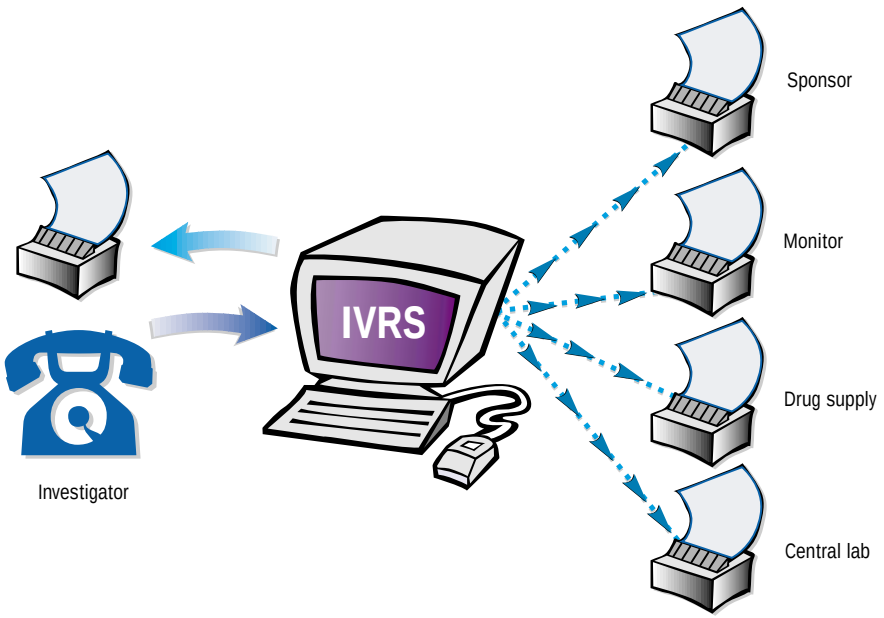

Figure 3. Users interact with an interactive voice response system by pressing keys on standard touch-tone telephones in response to prerecorded voice requests.

Centralized randomization

Minimization is a dynamic method that uses information on subjects already entered to allocate treatment to the next subject.[11] This requires continuous updating of the information related to previous treatment allocations, and is usually done through centralized randomization using a telephone, fax machine, computer, or the Internet. To implement centralized randomization, IVRS (interactive voice response system) technology has gained popularity in recent years. It is easy to use, reliable, inexpensive, multilingual, and accessible worldwide around the clock (Figure 3). The entry of subjects in a comparative clinical trial through an IVRS can trigger a whole sequence of events, including treatment allocation, choice of drug dose, subject inclusion reporting, control of site recruitment, management of clinical trial material inventory, and management

of subject and monitoring visits. IVRS is relatively cumbersome, however, especially when alphabetic (rather than only numeric) information must be entered. The Internet provides a more versatile environment to implement centralized services for clinical research. Portable devices such as hand-held PCs and smart phones may soon make centralized randomization easier than ever before.

The concept of a centralized randomization office has long been familiar to collaborative groups that use it to ensure that treatments are allocated properly as well as to keep tight control over a trial's progress.[12] Other ways of entering subjects in trials—such as providing all centers with preprinted lists of treatment allocations or with sets of sealed envelopes—are not foolproof and are therefore best avoided. With centralization, there is no need to maintain "double randomization" lists (one list linking subject numbers to treatments, the other linking medication numbers to treatments), because the list linking subject numbers to treatments can be generated dynamically.[3]

The most critical benefit of centralization is improved reliability of the randomization procedure and, consequently, of the trial results.[13,14] Centralized randomization offers several other benefits that may significantly improve the management of multicenter trials.

- The most important eligibility criteria can be checked in a uniform fashion across all centers.[15]
- The accrual of subjects in each center is monitored in real time, which permits corrective measures to be taken if some centers turn out to be slow recruiters.
- A fax (or e-mail) can be sent automatically to the investigational center to confirm and document the randomization, with copies to the trial sponsor, the trial monitors, a drug supply center, and a central laboratory (Figure 3).
- The system can assist in scheduling subjects and monitoring visits.
- The system can assist in managing the inventory of clinical trial materials—in particular the investigational drug(s). (This feature is most useful to avoid waste, because centers can be supplied with a minimum amount of drugs and automatically resupplied depending on actual subject accrual and follow-up, rather than on some predetermined schedule.)
- The system can monitor drug expiry dates and automatically issue drug usage reports.
- The system can be programmed for emergency treatment unblinding.
- Essential subject efficacy and safety data can easily be entered into the system if real-time access to such data is required (for example, in dose titration studies where the dose administered to the next subject depends on the outcomes of previously treated subjects).
- Treatment dose and schedule can be calculated based on subject characteristics or laboratory values (for example, in trials of cytotoxic therapies that are dosed according to body surface area and hematologic status).
- Every access to the system is fully documented as each call is recorded and stored in an audit trail for later checks, if required.

For all these reasons, it may be worth considering centralized randomization for every clinical trial of some importance or magnitude. The benefits of centralizing randomization (and, indeed, other aspects of trial management) may far outweigh the costs involved.

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