

Complex problems, simple solutions

With the increasing complexity of trial design comes greater logistical problems associated with managing trial supplies. **Bill Byrom, Damian McEntegart** and **Malcolm Morrissey** discuss how common technological solutions can help overcome drug supply constraints, shortages and possible unblinding

KEYWORDS: Trial supply; Randomisation code look-ahead; Zelen's method; Dose adjustment; Blinding

Over the past two decades, clinical trials have become larger, more complicated and increasingly global, and this trend is continuing. Multinational studies are now commonplace and conducted in a growing number of countries, all of which provide important access to patient populations and pre-approval exposure within potentially significant markets. As design and logistical complexities continue, technology plays an increasingly vital role in the effective implementation and management of today's clinical trials.

This article considers how the novel use of commonly used technology can assist in managing clinical trial supplies by considering two interesting application areas: strategies for conducting studies when medication is in very short supply; and methods of adjusting the dose based on a response endpoint while maintaining study blinding.

For each example we consider extensions to the use of central randomisation and trial supply management solutions. These solutions commonly use the telephone (interactive voice response – IVR) and the web (interactive web response – IWR) as a simple and ubiquitous interface between the central system and users. Before considering the examples, we briefly overview how these solutions operate in managing the logistics of randomisation and medication supply during a clinical trial.

Randomisation and supply solutions

IVR/IWR systems are used to manage randomisation, medication assignment, medication stock control and emergency code break. The use of centralised electronic methods to perform randomisation adds integrity to the randomisation process and enables certain methods to be employed which would traditionally be impossible or too complex for site staff to administer without risk of error.

Many large clinical trials use IVR/IWR systems to simplify the logistics of controlling medication stock across countries and sites involved in the study.

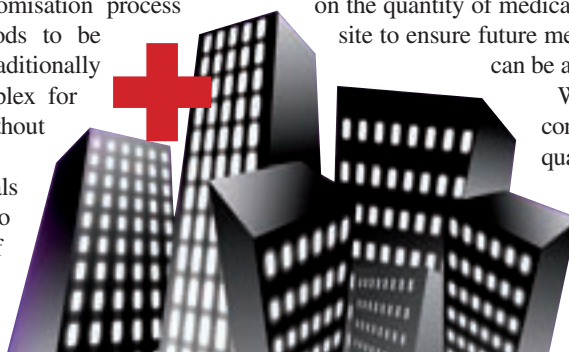
The IVR/IWR approach promises not only logistical simplification, but also savings in the quantity of medication overage required to conduct a trial. With this approach drug supplies are not packaged in patient numbered kits, but each dispensing unit of medication is assigned a unique numerical code. In a study where patients return for repeat dispensation this means a different pack is allocated at each dispensing visit. This increases flexibility in the use of supplies: any pack at site can be assigned to any patient within the appropriate treatment group; it is not necessary to store all packs potentially required by an individual patient up-front; and packs earmarked for patients that subsequently withdraw can be allocated to other patients within the same treatment group. These features mean the quantity of stock stored at each site can be minimised, and medication wastage due to patient withdrawals and low patient recruitment can be limited.¹

Problem 1: Supply shortages

While IVR/IWR systems are valuable in ensuring studies are conducted with the efficient use of supplies, there are occasions when supplies are particularly scarce or expensive. In these cases, particular methods can be considered to ensure medication is used most sparingly.

When selecting a randomisation approach, methods that ensure balance between treatment group allocations at each site have the additional advantage that site supply requirements are more predictable. When not balancing the randomisation at a site level it is possible, for example, to allocate all patients to a single treatment group. This has a significant impact on the quantity of medication required by each site to ensure future medication assignments can be accommodated.

When faced with constraints in the quantity of medication available, there are two randomisation methods that are recommended: randomisation code look-ahead and a



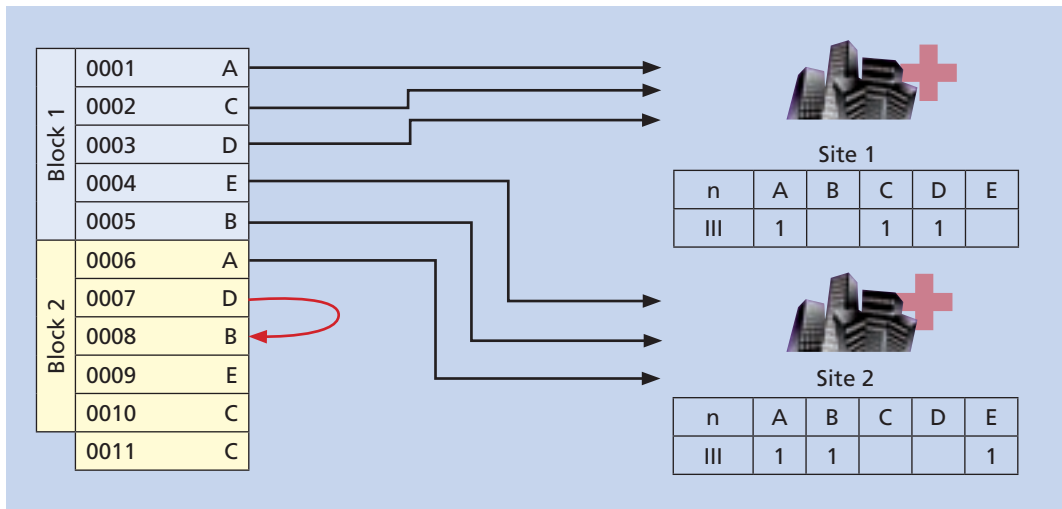


Figure 1: An example illustrating Zelen's method of randomisation.

variation of Zelen's method.² Each method can be explained and illustrated with reference to a five-treatment study, where patients are allocated to each treatment group in a 1:1:1:1:1 ratio at the site level.

1. Randomisation code look-ahead

In this approach, blocks of a pre-defined randomisation list are assigned in advance to each study site. If a block is simply a random combination of the five treatment groups, not only does a central randomisation system know that every five new randomisations at a site will involve one randomisation to every treatment, but it also knows *a priori* the order treatments will be allocated, enabling efficiencies in medication to be realised.

A typical site supply strategy might therefore be to initially send enough medication for the first three treatment allocations in the code list. Once two patients have been randomised at the site, the system will look ahead in the site-specific randomisation code blocks, determine which treatment allocations will be next, and restock the study site accordingly.

This method is very conservative in the use of supplies, and further savings can be made by only shipping medication based on screening activity at the study site. However, one disadvantage is that in assigning blocks to each study site it is likely that at the end of the study many sites will complete randomisation without getting to the end of their current randomisation block. Although the 1:1 ratio is maintained to within plus or minus one patient at each site, when sites are combined it is likely that overall there will be different numbers of patients assigned to each treatment. The degree of imbalance at the study level will depend on the block size and the sample size relative to the number of sites. In some cases, the possible degree of imbalance may be too high – making this method less desirable despite its medication-saving properties.

2. Zelen's method

Zelen's method also uses a pre-defined randomisation code list, but does not assign blocks to sites. Instead, medication assignments are determined with reference to a single code list.

Site balance, however, is maintained by skipping randomisation code entries if the chosen allocation would cause treatment imbalance at the site to exceed a pre-defined threshold.

In the example outlined in Figure 1, the first three patients randomised have been recruited at site one and assigned to treatments A, C and D respectively. The following three patients have been recruited by site two and assigned treatments E, B and A. We apply a constraint such that there can be no imbalance in treatment allocations at sites greater than one patient. Currently, we have an imbalance of one at each site (the most patients assigned to any treatment group is one, and the least is zero). Continuing the example, imagine the seventh patient to be randomised is recruited to site one. According to the code list, the next treatment allocation would be group D but that would cause the imbalance at the site to exceed the threshold (we would now have two patients assigned to D compared to zero on B and E). Zelen's approach involves skipping this treatment assignment and continuing down the randomisation list until one can be found that satisfies the site-balance constraint. In this case, the next code entry (0008) is treatment B. This meets our site-balance conditions and so is the treatment allocation selected.

As randomisation continues, we extend Zelen's method to consider available treatment assignments in order, including any skipped randomisation code. Thus, in our example, if the next patient randomised belongs to site two, then the patient will be assigned to the recently skipped randomisation code entry (0007: D).

The example illustrates that when using Zelen's method it is possible to maintain both site- and study-level balance. However, although it is clear that every five patients recruited at the site will be assigned one to each treatment group, it is not possible to know the order in which those treatment groups will be assigned. This has an impact on medication supply strategy. In the example above, we must supply five packs (one of each treatment group) to each site initially. When the number of packs at a site falls to a predefined minimum (for example, one pack) the site will be resupplied with another five packs (again, one

of each treatment group). Random packs may also be included within shipments to disguise the block size.

While both approaches discussed are conservative, randomisation code look-ahead is the most sparing, but may result in an overall study imbalance in treatment allocations. Zelen’s method protects against study imbalance but at the expense of being slightly less conservative in the quantity of medication required. Theoretically there may be special statistical analysis considerations associated with Zelen’s method but practically these should not apply. Thus the choice of method depends on just how scarce or expensive the medication is and how big an impact an overall treatment imbalance at the study level might be. The optimal method can be best determined using simple simulations in the protocol-design stage.

Problem 2: Titrating to clinical response

Some complex clinical trials require medication to be adjusted relative to an observed clinical endpoint. When this endpoint is only observed or affected by one treatment group, ensuring treatment allocations are kept blinded to those conducting the study presents a major challenge for trial designers.

A good example is in stroke and cardiovascular studies where a placebo or comparator group is compared to warfarin, or a combination including warfarin. Warfarin is an anticoagulant, and its blood-thinning effects are measured by prothrombin time. This is commonly expressed as an international normalised ratio (INR) value, and routinely measured to ensure patient safety. Typically this therapeutic range is $2 \leq \text{INR} \leq 3$, although it may differ within some patient groups. In routine care, INR values are calculated using a point-of-care device that provides an instant INR estimate from a single drop of blood – much like a blood glucose device used by diabetic patients.

In a clinical trial, it is essential that the investigator knows the INR value for any warfarin patients, so their optimal dose can be maintained and their safety assured. However, for the integrity of the study it is also essential that site personnel cannot distinguish between warfarin-treated patients and those in other treatment

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groups. This issue as it relates to antithrombotic trials has been recently discussed by regulators.³

To address this, modifications to the point-of-care device are made so that instead of directly providing an INR value, the device outputs an encrypted code. This masks the true INR reading for all treatment groups. To calculate the INR value, the investigator must provide the encrypted code to the IVR/IWR system, which will then return the true INR value for a warfarin-treated patient or a mock value for placebo/comparator patients. The mock values reported will not correspond to the INR value from the encrypted code. The objective here is to ensure that the mock INR values are generated in such a way that it would be impossible to guess whether they apply to a warfarin patient or one assigned to another treatment.

To ensure blinding is maintained, the site would have to ‘raise’ or ‘decrease’ the placebo or warfarin dose in accordance with the INR value given by the IVR/IWR system. This would be achieved by allocating a new treatment pack to patients requiring a dose adjustment, but in the case of non-warfarin patients this would be a mock adjustment and would simply contain the existing dose. Figure 2 illustrates how this approach would be implemented in a clinical trial.

The art of this approach is in generating mock INR values in such a way that they mimic the properties of the true values well enough to prevent accurate guesswork by those conducting the trial.

There are a number of possible methods commonly used to generate mock INR values. The simplest

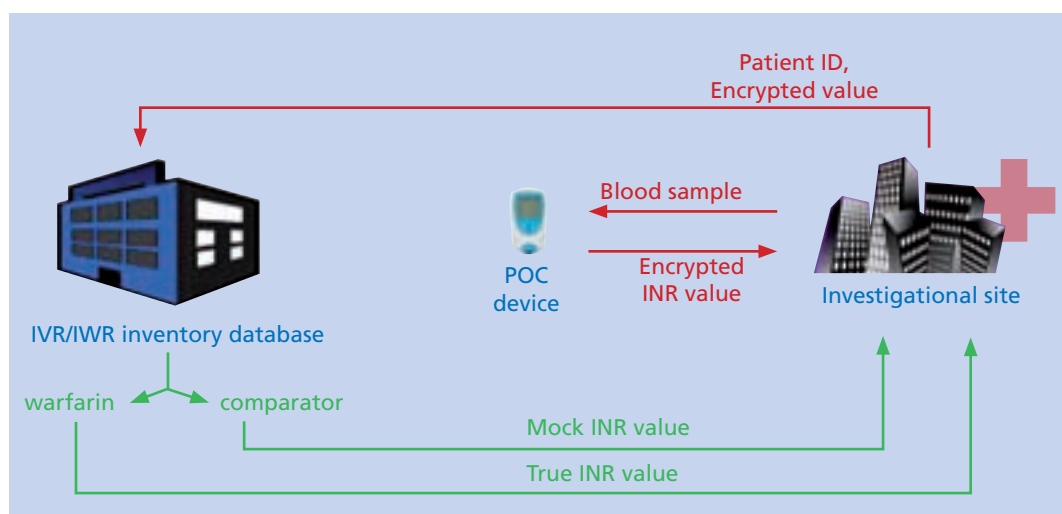


Figure 2: An example illustrating the provision of true and mock international normalised ratio (INR) values to maintain study blinding.

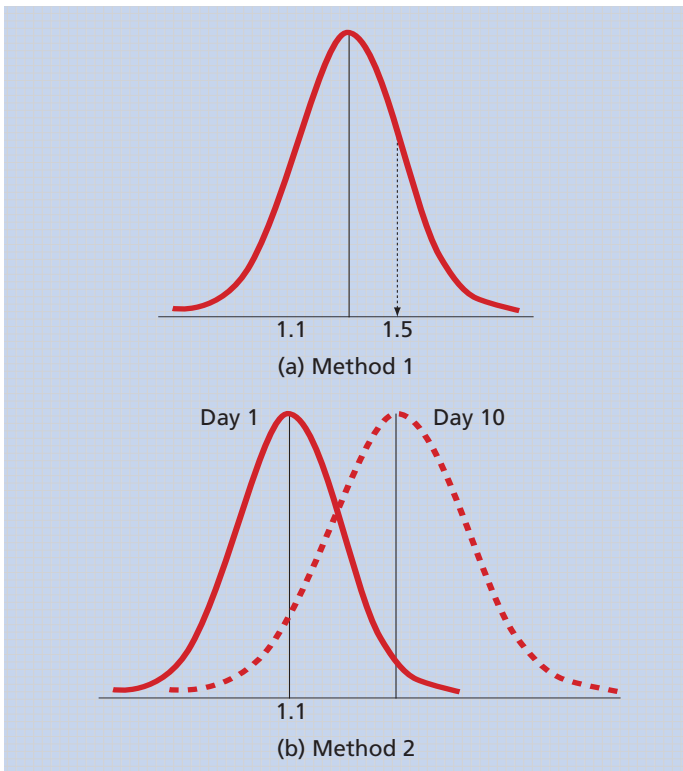


Figure 3: Methods illustrating the generation of international normalised ratio (INR) values from a) a single distribution and b) a distribution that changes over time.

method (method 1 in Figure 3) uses the known distribution of INR values (estimated using previous or published data) and randomly samples a value from this distribution for each mock value required. This is simple, but as an INR is likely to change over time due to treatment, this ignores the expected autocorrelation between INR values within a subject and could lead to an increased ability to guess the treatment group by inspecting the variability and trend of the INR values obtained for individual patients.


A second method (see Figure 3) protects against this. By estimating the distribution of INR values for each time point (again based on previous or published data) it is possible to mimic the trend in INR values expected for patients receiving warfarin. On each occasion, a random INR value is selected based on the distribution specific to that day of treatment. Enhancements to these approaches might include calculating different distributions for important patient sub-groups, such as age and gender, and considering the effects of current dose levels.

Another approach is to use the IVR system to randomly select from a set of pre-determined schedules as in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial.⁴ Clearly there should be many schedules available to choose from to avoid pattern recognition.

Finally, mock INR values can be generated based upon multiple regression models, taking into account the factors important in influencing an INR amongst warfarin-treated patients. In a typical model developed using historical data, a mock INR value might depend upon patient factors, such as age, gender, dose (assumed dose), previous INR values and phase of therapy.⁵

The choice of method is not limited by technology, as each can be applied in a straightforward way by an IVR/IVR system. This choice is ultimately the study team's and depends on which they feel will limit the ability of investigators and sponsor personnel to correctly guess the treatment allocated to individual patients on the basis of study INR data. This example is not unique. The challenge is common to any indication in which dose adjustments are required based on a response endpoint, and where different treatments may affect the endpoint in different ways.

Conclusion

This article has aimed to illustrate how technological solutions responsible for randomisation and trial supply management can be used to solve challenges posed by some of today's complex study designs. More often we are seeing increased complexity and logistical challenges in protocols. Adaptive trials, along with other complex designs, plus the requirement to conduct studies faster, with less medication and in more remote parts of the world all add to the complex environment in which we operate. Today's clinical trial technology solutions are evolving to meet these challenges. 

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