

Complex Randomisations Need Not Be Complex

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Introduction

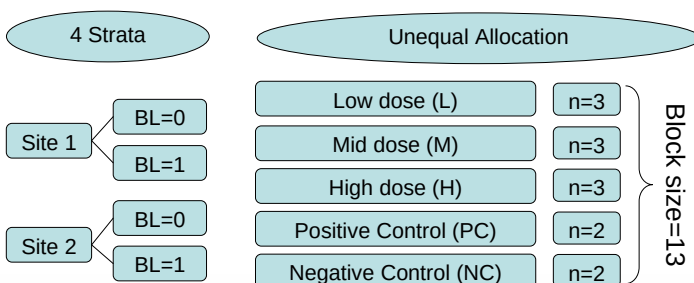
Unbalanced allocations to treatment are rarely employed within randomised clinical trials (e.g. only 2.3% of studies in the MEDLINE database from 1991-1995) as normally equipoise is assumed in that there is sufficient uncertainty of whether one treatment arm is superior to another (Avins, 1998).

Unequal allocations may be considered for various reasons, such as:

- Learning more about the experimental compound (as in our case);
- Ethical grounds;
- Will only adversely affect the power if ratio is >3:1 (Pocock, 1983);
- Differing costs between treatment arms;
- Anticipated higher drop out rate in one group (thereby enhancing the power for a per-protocol analysis) (Dumville, 2006).

The Task

A randomisation was required for a Phase 2 proof of concept study with 5 arms in a 3:3:3:2:2 allocation. Sample size calculations indicated that a total of 234 subjects should be enrolled (54:54:54:36:36). The randomisation was to be stratified by site and a binary baseline (BL) characteristic (i.e. 4 strata) so that at any one snapshot of time, the allocation should be as close to 3:3:3:2:2 as possible, overall and within strata. An interim analysis (IA) was planned at 50% completed subjects.



The Solution

Treatments L, M, H, PC and NC in 3:3:3:2:2 allocation ratio gives a block size of 13. Create 3 types of sub-blocks within the main block:

- Sub-block A: 1:1:1:1:1
- Sub-block B: 1:1:1:1:0
- Sub-block C: 1:1:1:0:1

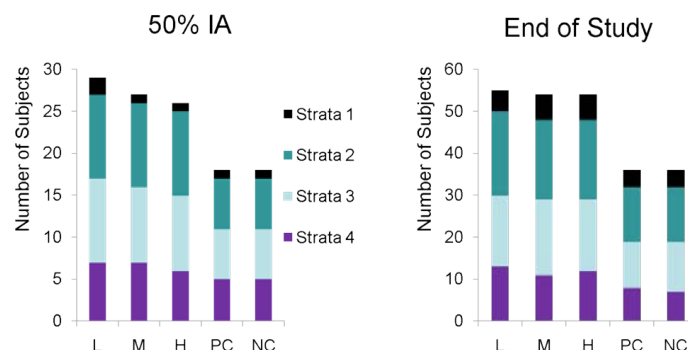
Randomisation part 1: Randomise the order these sub-blocks appear within the main block

- ABC, ACB, BAC, BCA, CAB, CBA

Randomisation part 2: Within each sub-block, randomise the order of each treatment (L, M, H, PC and NC).

Results: 50% IA and End of Study

IA and end of study analyses were performed with 118 patients and 235 patients (1 was a replacement), respectively. The allocation achieved was close to the expected allocation to active dose and control groups at interim (27 and 18, respectively) and end of study (54 and 36, respectively).



Implementation

Although not possible using in-house standard randomisation systems at the client, the above is easily programmed within SAS (see handout).

Once performed, the final randomisation was uploaded into the client system.

Randomisation lists were cascaded to the pharmacy at the sites, where treatment was prepared for administration as and when required (minimising overage). The randomisation lists made provision for 234 within each strata, should only one of the four strata be able to recruit.

The above could easily and simply be extended to later phase studies, where product is already prepared and sat on the shelf.

Conclusion

Seemingly complicated designs with unbalanced allocation ratios, can be broken down into smaller size tasks.

By simplifying the 3:3:3:2:2 allocation ratio into 3 more manageable sub-blocks, and randomising the order these 3 sub-blocks come in, within the main block, ensures that at any snapshot in time, within and across strata, the allocation ratio would be adhered to as closely as possible.

References

- Avins, AL. 1998. *Can unequal be more fair? Ethics, subject allocation, and randomised clinical trials.* J Med Ethics; 24:401-408.
- Dumville JC, et al. 2006. *The use of unequal randomisation ratios in clinical trials: a review.* Contemp. Clin. Trials; 27(1): 1-12
- Pocock, SJ. 1983. *Clinical trials: a practical approach.* Chichester: John Wiley & Sons Ltd.