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Complex Randomisations Need Not Be Complex

Fiona Brock, Quanticate Ltd, Hitchin, UK

ABSTRACT

In collaboration with a client, we designed a trial with five treatment arms: three were various doses of the active compound, one arm was a positive control and the final arm was a negative control. It was desired to have an unequal allocation to treatment: 3:3:3:2:2. The sample size was 234 patients, enrolled at two sites; patients were additionally stratified according to a baseline (binary) characteristic. An interim analysis was planned, and we needed to ensure that at any snapshot in time, the allocation ratio adhered to the 3:3:3:2:2 as closely as possible.

This paper examines why we would have unequal allocation to treatment in the first place, and how to go about performing a randomisation such that for any interim snapshot, we could ensure as balanced as possible allocation overall. Additionally we present how close we were to the allocation ratio, when the interim analysis was performed.

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) since equipoise is normally assumed in that there is sufficient uncertainty of whether one treatment arm is superior to another (Avins, 1998).

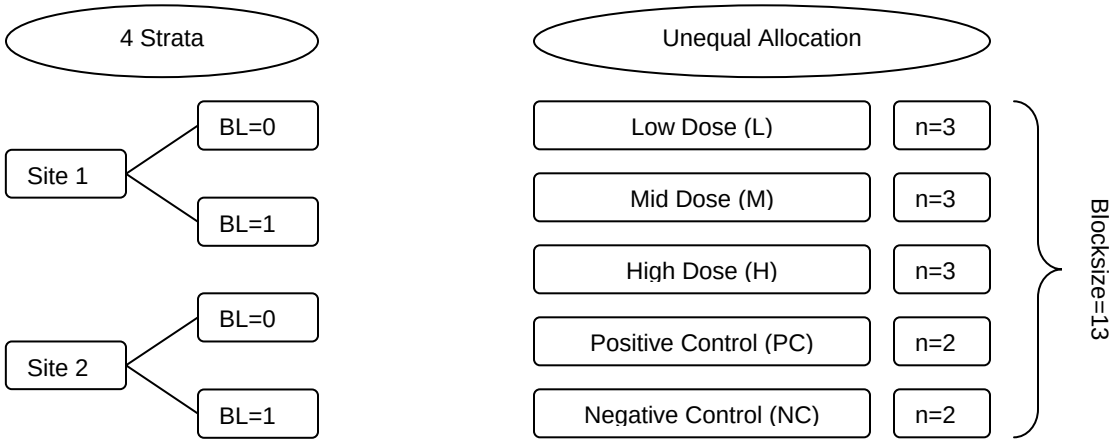
Unequal allocations may be considered for various reasons, such as:

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

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, as depicted in Figure 1. An interim analysis (IA) was planned at 50% completed subjects.

FIGURE 1: STRATIFICATION AND ALLOCATION WITHIN STRATA



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

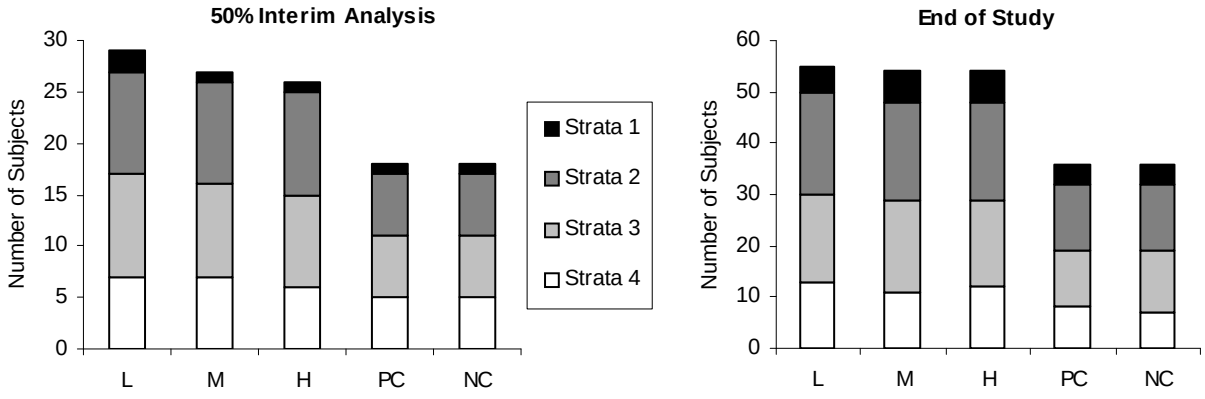
Randomisation part 1: Randomise the order these sub-blocks appear within the main block
ABC, ACB, BAC, BCA, CAB, CBA

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

RESULTS: 50% INTERIM ANALYSIS AND END OF STUDY

Interim analysis 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), as given in Figure 2.

FIGURE 2: NUMBER OF SUBJECTS AT 50% INTERIM ANALYSIS AND END OF STUDY



IMPLEMENTATION

Although not possible using in-house standard randomisation systems at the client, the above is easily programmed within SAS®, as in the below:

```
** X1=random seed for the order in which the sub-blocks appear in, within each main block **;
** X2=random seed for the order in which the treatments appear within each sub block **;
%let x1=8705029;
%let x2=4710943;
```

```
data rando1;
  ** 18 blocks, per site, per baseline (binary) characteristic = 72 blocks **;
  do mainblk=1 to 72;
    ** 3 types of sub-block within each block **;
    do blkorder=1 to 3;
      x1=ranuni(&X1);
      output;
    end;
  end;
run;

proc sort data=rando1;
  by mainblk x1;
run;

data rando2 (drop=x1);
  set rando1;
  by mainblk x1;

  ** assign which blocks go to which site and baseline characteristic **;
  ** since everything else is randomised, no need to randomise this too **;
  if mainblk le 18 then do; site=1001; blsev=0; end;
  else if mainblk le 36 then do;
    site=1001; blsev=1;
  end;
  else if mainblk le 54 then do;
    site=1002; blsev=0;
  end;
  else do;
    site=1002; blsev=1;
  end;

  ** sub-blocks are now randomly ordered within mainblock (based on x1 random value) **;
  if first.mainblk then subblk=1;
  else if last.mainblk then subblk=3;
  else subblk=2;

  ** expand each sub-block by the treatment combinations **;
  ** in the next datastep we randomise the order these will appear in, within the sub-block**;
  attrib trt length=$10 label='Treatment code';
  if subblk=1 then do; ** sub-block type A **;
    trt='A'; output; trt='B'; output; trt='C'; output; trt='D'; output; trt='E'; output;
  end;
  else if subblk=2 then do; ** sub-block type B **;
    trt='A'; output; trt='B'; output; trt='C'; output; trt='D'; output;
  end;
  else if subblk=3 then do; ** sub-block type C **;
    trt='A'; output; trt='B'; output; trt='C'; output; trt='E'; output;
  end;
run;

data rando3;
  set rando2;
  x2=ranuni(&X2);
run;

proc sort data=rando3;
  by site blsev mainblk blkorder x2;
run;

data rando4 (drop=x2);
  attrib randnum length=8. label='Randomization number'
         blsev length=8. label='Baseline characteristic'
         orderwistrata length=8. label='Enrolment order within strata';
  set rando3;
  by site blsev mainblk blkorder;
  if first.blsev then orderwistrata=1;
  else orderwistrata+1;
  if site=1001 then do;
    if blsev=0 then randnum = 11000 + orderwistrata;
    else if blsev=1 then randnum = 12000 + orderwistrata;
  end;
  else if site=1002 then do;
    if blsev=0 then randnum = 13000 + orderwistrata;
    else if blsev=1 then randnum = 14000 + orderwistrata;
  end;
run;
```

Once performed, the final randomisation and dataset were 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.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Fiona Brock
Quanticate Ltd
Bevan House
Bancroft Court
Hitchin
Hertfordshire SG5 1LH
UK
Work Phone: 0044 (0) 1462 440084
Email: fiona.brock@quanticate.com
Web: www.quanticate.com