Case Studies Using Dynamic Randomisation Techniques other than Minimisation

EFSPI meeting on Adaptive Randomisation

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Agenda

- Demand for different types of dynamic randomization

- Dynamic balancing randomisation
  - the method
  - case study

- Zelen's method "balanced blocks"
  - medication supplies in IVR systems
  - the method
  - case study

- Regulatory interactions

Dynamic randomisation techniques

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Dynamic randomisation techniques

- ClinPhone has done over 350 studies using a dynamic randomisation technique
- Last 10 years, minimisation has comprised 80% of these
- Last year, minimisation comprised 50%
- Others have included:
  - dynamic balancing
  - zelen's method extension
  - urn methods
  - methods accounting for continuous scale variables (e.g Frane DIJ 1998, Endo CCT 2006)
- We haven't done Atkinson optimum designs
  - clients haven't asked for-too complex
  - balancing per se is more important than power
  - if centre is a factor then loses most of small power advantage

Dynamic balancing randomisation

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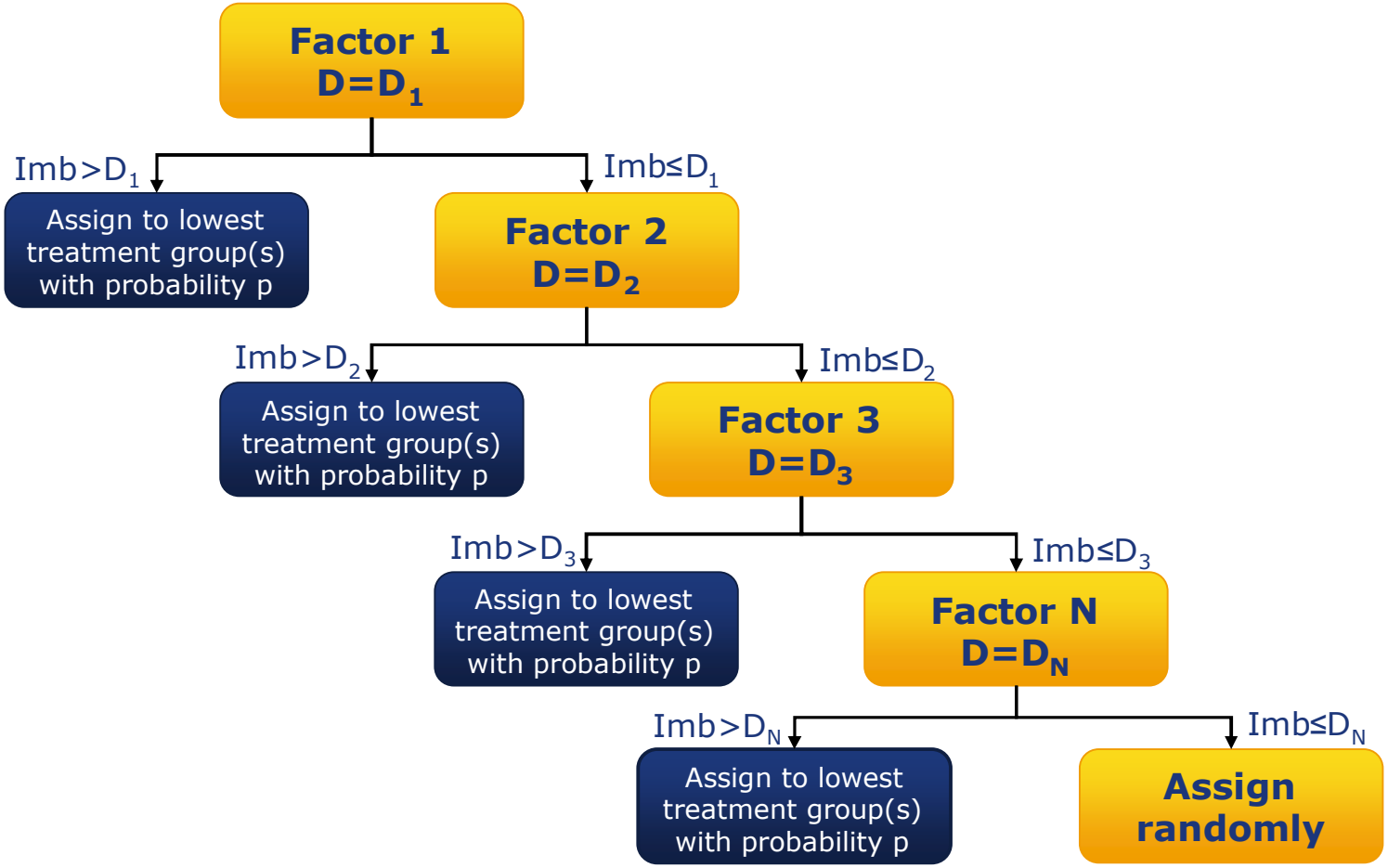
Dynamic balancing randomisation (DBR)

- Origins lie in Signorini's hierarchical method (SIM 1993)
- Variant offered by ClinPhone since 2001
- Use has taken off since publications in 2005
  Heritier SIM
  Borm CCT
- Now used almost as much as minimisation

DBR methodology



DBR advantages

- Simplicity?
- Favourably received by some FDA reviewers
- More allocations made entirely at random than minimisation according to Heritier for marginal decrease in power
- Balancewise not much difference between the methods if use appropriate weights in minimisation

Heritier 2005 simulation (1)

- Example 1: Small trial of 200 patients

- 3 strata
  Gender: 2 levels $D_1=2$
  Age : 3 levels $D_2=3$
  Site : 4 levels $D_3=4$
  Overall :1 level $D_4=5$

- No random element unless falls through to last level in DBR

- Standard unweighted minimisation as comparison –no random element unless a tie

- Performance measures
  Loss – the loss of information due to imbalance expressed as number of patients
  Forcing index- proportion of deterministic allocations

- 1000 simulations were performed

Heritier simulation (2)

- Minimisation.
  Median loss=0.1, %deterministic allocations=79%

- DBR.
  Median loss=0.7, %deterministic allocations=42%

  Note average loss for simple randomisation followed by stratified analysis by ANOVA would be 6

- Same results in other simulation experiments

- So possibly in the trials we perform with a random element there will be less use of biased coin (e.g. 80:20) in DBR than minimisation and more use of fair coin (50:50)

- Would have to be confirmed by simulation for trial in question

ClinPhone Case Study 1

- Phase 2 trial in neuropathic pain with adaptive design and two phases
- 160 subjects in first phase, 200 subjects in second phase
- 30 sites
- 4 treatments in first phase: placebo or one of three dose levels.
- Chosen dose and placebo in second phase
- Dynamic balancing used to randomise subjects to Factors

Baseline pain (IVR ePRO) 0-3, 4-6, 7-10	$D_1=2$
Site	$D_2=2$
Gender M, F	$D_3=3$
Study	$D_4=2$

  D values determined with aid of simulation
- Random element=0.85

Case Study 1 (continued)

- Interim analysis after 160 subjects
- Recruitment allowed to continue while analysis in progress
- Sponsor drops 2 doses via an automated call to the IVR system.
- Counts from placebo and chosen dose in first phase are included in counts used in second phase.
- Thus balance assured throughout the trial
- IVR automated supply chain using non-informative pack numbers and so investigators will be unaware when the doses are dropped

Why use DBR in this design?

- Evidence from literature that all factors were good prognostic factors
- Strong site effect seen in previous study particularly for adverse events
- Wanted to maximise chances of correct decision at interim analysis
- DBR preferred to minimisation due to clear hierarchy of factors in sponsors eyes
- Simulations used to explore effects on balancing of various values of $D_1 \ldots D_4$ and random element
- Carrying forward of counts ensured balance over both phases combined

Zelen’s technique

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ClinPhone Case Study 2

- Phase 2 trial
- 300 subjects.
- 60 sites
- Single administration of medication
- Medication costs £1,000 per administration
- Slow recruitment so don't want to limit number of sites or numbers at each site – competitive recruitment

Randomisation and Supply options (1) Traditional scheme

- Traditional patient numbered packs distributed to sites according to site blocked randomisation with block size of 5
- Send initial block of 5, resupply another block when 3 patients recruited
- Issue (in client's mind) is potential imbalance at study level
- 1000 simulations of range of overall treatment allocations
- Mean=7.6 SD=2.9 max=21
- Example of imbalance of 8 =61, 65, 69, 62, 63
- Example of imbalance of 21=67, 51, 66, 72, 64
- So sponsor decided against traditional site randomisation and pack #s

Medication Management
IVR/web approach

- Unique Medication Numbering
  - Can be applied to 'Kit' of supplies
  - Can be applied to the Individual Dispensing Unit
- Any unit can go to any patient (conditional on randomised group)
- Any unit can be used for any treatment period
- Using the smallest dispensing unit gives the most flexibility

Randomisation and Supply options (2) IVR unstratified randomisation

- Use unstratified randomisation list with allocation by IVR
- Use IVR automated medication inventory management to manage supplies at site
- Initially send 2 packs of each treatment
- As soon as the site inventory of any pack is down to 0, automatically request depot to top up all the packs so that there are 2 packs of each treatment
- Note in the period when packs are being delivered, if unlucky a patient could be randomised to a treatment for which there are not packs at site

Dynamic Allocation

IVR variant of Zelen's 1974 General Method

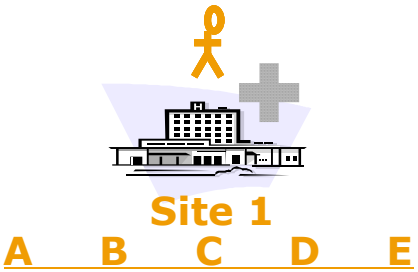
- Dynamic scheme although uses a randomisation schedule
- Consider example of 2 treatments
- Site imbalance to remain ≤ D (e.g. D=2)
- Assess new Site imbalance for next entry to be assigned
- If new Site imbalance is <=D then assign this entry
- If new Site imbalance is >D then assess imbalance for next entry; continue until entry assigned for which imbalance <=D

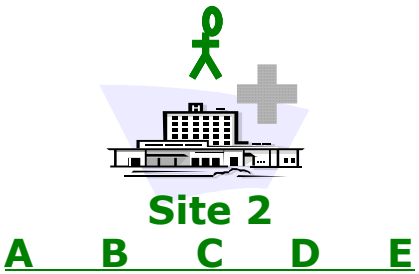
Randomisation and Supply options (3) IVR and Zelen's method

- Use unstratified randomisation list with block size of 5
- Allocate first unused code on list that does not cause range of treatment allocations at site to exceed 1 (D=1).
- Codes will sometimes be skipped over but are always available for future allocations
- In effect the method is dynamically constructing site stratified blocks of 5. The block construction is taking the study level balance into account.
- Maximum range at any point in study is 4. Optimum site balance as using site stratified blocks

Randomisation and Supply Options (3)

Zelen's Method with D=1





RANDNO	TREAT GROUP	BLOCK	TREAT BALANCE	SITE	PATNO
0001	A	1	1,0,0,0,0	1	001001
0002	C	1	1,0,1,0,0	1	001002
0003	D	1	1,0,1,1,0	1	001003
0004	E	1	0,0,0,0,1	2	002001
0005	B	1	0,1,0,0,1	2	002002
0006	A	2	1,1,0,0,1	2	002003
0007	D	2	1,0,1,2,0		
0008	B	2	1,1,1,1,0	1	001004
0009	E	2			
0010	C	2			
…	…		…	…	…

Supplies using Zelen's method

- Can use knowledge of site stratification
- Send 5 packs (one of each type) to each site
- Automatically send next set of 5 when 4 patients recruited

Simulation results

Quantity	Method 2 Unstratified randomisation			Method 3 Zelen Randomisation		
	Mean	SD	Max	Mean	SD	Max
Range of trtment totals	0	0	0	1.3	1	4
Total # packs shipped	817	9	844	537	11	570
% packs wastage	172	3	181	79	4	90
# ship-ments	127	4	138	107	2	114

Zelen's method considerations

- Has enabled use of site stratified randomisation where otherwise sponsors might not think it desirable due to study level balance considerations
- As it was used with automated supply chain management then it is saving scarce & expensive supplies
- Concern over block size of 5 and predictability?

Zelen's method analysis considerations

- Strictly speaking need to account for centre in the analysis
- But there is some flexibility on this where stratification is for logistical reasons and #s patients per centre are low
- As the actual scheme used will be a valid sample from a conventional application of site blocked randomisation then conventional analysis can arguably be used?
- But blocks are not sampled independently
- Although a randomisation list is being used, it is a dynamic allocation technique based on counts of prior allocations
- MHRA (Ian Hirsch) considers that a re-randomisation test is needed as a sensitivity analysis if trial is pivotal, "probably not" otherwise

Regulatory interactions

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Regulatory interactions

- In 350+ dynamic allocations studies not much!
- Figures below not won't be exact-just the ones we know of
- FDA
  - asked client to alter random element (5 times)
  - asked for weighting justification (3 times)
  - asked for re-randomisation test (3 times)
  - advised client to use static scheme (3 times)
  - advised client to use a dynamic scheme (2 times)
- Europe
  - literature debate in ACT
  - asked client to justify scheme (2 times)
  - stated need for re-randomisation test if trial is pivotal (1 time)

ClinPhone position on dynamic randomization methods

- Often IVR is being used for supply chain management or ePRO and cost/benefit considerations on choice of randomisation method should be done on marginal cost
- MHRA point about more complexity leads to higher risk of errors but should not be true of validated system.
- Insurance against imbalance that might damage trial credibility and complicate interpretability
- If trial is pivotal, carefully consider the CPMP guidance
- Balancing factors must be well founded
- Scientific justification not too difficult if balance at site level and 1 or 2 co-factors is warranted
- Client should be aware of risk that may need re-randomisation test

References

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**** available on www.clinphone.com**

Any Questions?

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