Case Studies Using Dynamic Randomisation Techniques other than Minimisation

EFSPi meeting on Adaptive Randomisation
7th December 2006

Damian McEntegart, Head of Statistics, ClinPhone plc
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
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
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

Factor 1
\[ D = D_1 \]
- \( \text{Imb} > D_1 \):
  - Assign to lowest treatment group(s) with probability \( p \)
- \( \text{Imb} \leq D_1 \):
  - Factor 2
  \[ D = D_2 \]
  - \( \text{Imb} > D_2 \):
    - Assign to lowest treatment group(s) with probability \( p \)
  - \( \text{Imb} \leq D_2 \):
    - Factor 3
    \[ D = D_3 \]
    - \( \text{Imb} > D_3 \):
      - Assign to lowest treatment group(s) with probability \( p \)
    - \( \text{Imb} \leq D_3 \):
      - Factor N
      \[ D = D_N \]
      - \( \text{Imb} > D_N \):
        - Assign to lowest treatment group(s) with probability \( p \)
      - \( \text{Imb} \leq D_N \):
        - Assign randomly
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
  - Site
  - Gender M, F
  - Study
  - 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 $D_1...D_4$ and random element
- Carrying forward of counts ensured balance over both phases combined
Zelen’s technique
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

<table>
<thead>
<tr>
<th>RANDNO</th>
<th>TREAT GROUP</th>
<th>BLOCK</th>
<th>TREAT BALANCE</th>
<th>SITE</th>
<th>PATNO</th>
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<tbody>
<tr>
<td>0001</td>
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<td>001001</td>
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<td>C</td>
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<td>1</td>
<td>001002</td>
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<td>1</td>
<td>001003</td>
</tr>
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</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Method 2 Unstratified randomisation</th>
<th>Method 3 Zelen Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Range of treatment totals</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total # packs shipped</td>
<td>817</td>
<td>9</td>
</tr>
<tr>
<td>% packs wastage</td>
<td>172</td>
<td>3</td>
</tr>
<tr>
<td># shipments</td>
<td>127</td>
<td>4</td>
</tr>
</tbody>
</table>
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
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

- **Dynamic balancing**
  Heritier et al. Stats in Medicine 2005;24:3729-3741
  Borm et al. Contemp Clin Trials 26 2005;26:637-645

- **Other dynamic balancing techniques**
  **McEntegart Drug Information Journal 2003 ;37;293-308**
  Endo Contemp Clin Trials. 2006 ; 27:420-431

- **Zelen’s technique**
  Zelen Journal of Chronic Disease 1974;27: 365-375
  **McEntegart et al. ISPE Pharm Engineering 2005 Sept/Oct ;36-46**

- **Forced randomisation in IVR**
  **McEntegart Applied Clinical Trials 2003;12(10):50-58**

- **Medication supply forecasting and simulations**
  **McEntegart et al Applied Clinical Trials 2004 ;13(7):40-46**

** available on www.clinphone.com
Any Questions?
dmcenteg@clinphone.com