Minimisation – Reducing Predictability Whilst Retaining Balance Within Centre

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Overview

• Scope of research
• Aims & Objectives
• Methods
• Results
• Conclusions
Scope of Research

Due to recent controversy, we investigated predictability of treatment allocation when randomisation is via minimisation (deterministic dynamic allocation)
Guidelines

- Committee for Proprietary Medicinal Products (CPMP) ‘Points to Consider’ –
  ‘dynamic allocation is strongly discouraged’

- ICH E9 Guidelines –
  ‘deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation’
Results of Hills (2003)

- Predictability by clinician is high when clinician included as a stratification factor
- Predictability significantly reduced when clinician not included
- Recommend clinician is not included as a stratification factor
Aims & Objectives

• Consider methods of reducing predictability by centre/clinician
• Consider within-centre imbalance
• Identify optimal minimisation method for reducing predictability whilst retaining sufficient balance within centre
Methods of Reducing Predictability

- Exclude centre as a minimisation factor
- Incorporate a random element, \( p \), into minimisation algorithm
  \( p = 0.95, 0.90, 0.80, 0.75, 0.70 \)
Methods of Assessing Predictability

- Consider real data from 6 multi-centre clinical trials
- Simulate treatment allocation over 1000 times
- Consider predictability methods according to Hills (2003)
Prediction Methods

- **M1** Predict alternative to that previously allocated
- **M2** Based on ALL previous allocations to that centre, predict treatment group with least number of patients
- **M3** As in M2 but based on previous 5 allocations only
Methods of Assessing Predictability

• Compare average predictability rates per trial with those of deterministic minimisation, i.e. no random element, where centre is included as a minimisation factor
## Datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>N</th>
<th>No. factors</th>
<th>No. centres</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>1380</td>
<td>4</td>
<td>43</td>
</tr>
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<td>3</td>
<td>794</td>
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<td>3</td>
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<tr>
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<td>128</td>
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<td>27</td>
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</table>
Results Under Deterministic Minimisation

• Average predictability over all predictability methods as high as 65%
• Maximum within-centre imbalance of 4 patients
Not Including Centre as a Minimisation Factor

• Maximum reduction in predictability – 9.1%

HOWEVER…

• Maximum within-centre imbalance of 36 patients
• Large imbalances may have logistical implications for centres
Incorporating a Random Element

- Consider average predictability per trial
- Consider maximum predictability per trial
- Compare maximum with that under simple randomisation
## Incorporating a Random Element

<table>
<thead>
<tr>
<th></th>
<th>Random Element</th>
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<tbody>
<tr>
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<tr>
<td>Max. average predictability (%)</td>
<td>65.2</td>
</tr>
<tr>
<td>Max. reduction (%)</td>
<td>-</td>
</tr>
<tr>
<td>Min. reduction (%)</td>
<td>-</td>
</tr>
<tr>
<td>Max. within-centre imbalance</td>
<td>4</td>
</tr>
</tbody>
</table>

EFSPI Adaptive Randomisation December 2006
## Incorporating a Random Element

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Max. predictability rates</th>
<th>Minimisation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Simple rand</td>
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<td>75.6</td>
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</tr>
<tr>
<td>6</td>
<td>72.7</td>
<td>76.3</td>
</tr>
</tbody>
</table>
Incorporating a Random Element

- $p=0.70$ gives best reduction in predictability however imbalance is high
- Max. imbalance when $p=0.80$ is only 3 more than max. imbalance under deterministic allocation, and reduction in predictability of at least 4.6%
- $p=0.80$ - optimum random element
Summary of Results

• Not including centre as a minimisation factor incurs large within-centre imbalance
• Introducing a random element reduces predictability
• Random element $p=0.80$ reduces predictability whilst retaining acceptable imbalance
Do Clinicians Predict Treatment Allocation?

• We asked 25 clinicians / research nurses, identified via the Trials Unit’s database, the following questions:
  – Do you predict treatment allocation?
  – Is there a method that you use to predict?
  – What are the reasons behind your decisions?
Responses

• 21/25 stated that they did not predict
• Reasons for not predicting included:
  – Incurs bias
  – Unaware it was possible
  – Unethical
• For those who did predict, method was to keep a log of previous allocations, which is keeping with the prediction methods we considered
Conclusions for Multi-centre Trials

• Include centre as a minimisation factor if imbalance is of concern logistically
• Incorporate a random element into the minimisation algorithm – p=0.80 is our recommendation
• Specify that centres should recruit more than 15 patients to minimise possibility of high predictability rates

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