Dynamic allocation

How to stratify if you must

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Dynamic Allocation: Balancing Act

- Some anecdotal history
- Some issues and a model
- Evaluation
- And now.....
Anecdotal history

PtC on Adjustment for Baseline Covariates final versus draft


“In our view, the CPMP’s position is unfair, unfounded, and unwise.”

“Achieving Balance in Clinical Trials.” Day, Grouin, Lewis. ACT, Jan 05.

“To say the guidance does not cite any references to support its views is an irrelevant argument.”

“If B’s and M’s criticism were to be “fair”, then on this basis they would also have to reject all the advice written in regulatory guidance with which they do agree.”
Randomisation

- The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias (ICH).
- “...having used a random allocation, the sternest critic is unable to say when we eventually dash into print that quite probably the groups were differentially biased through our predilections or through our stupidity.”
- Generation of allocation sequences
### Dynamic allocation

#### Covariate adaptive allocation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Group A</th>
<th>Group B</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>&lt; 30</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥ 30</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Chol</td>
<td>≤ 6.0</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 6.0</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Total allocated: 8 (A) + 9 (B) = 17

New -> A: \[ \text{Diff} = |5-5| + |5-3| + |4-2| = 4 \]

New -> B: \[ \text{Diff} = |4-6| + |4-4| + |3-3| = 2 \]

Random element: probability of assignment \(p\)
Dynamic allocation

How to stratify if you must........

Dynamic allocation vs Stratified Blocks

(where simple randomisation may do the trick as well)
Randomisation based inference

Two samples:

\[ X_1, X_2, \ldots, X_m \text{ and } Y_{m+1}, Y_2, \ldots, Y_{m+n} \]

\[ X_i = u_i + V_i, \quad Y_i = u_i + V_i \]

\( u_i \) is associated with the i-th subject

\[ E(X_i) = u_i + \xi, \quad E(Y_i) = u_i + \eta \]

\( V_i \) with drug & circumstances

Subjects (represented by \( u_i \)) do not constitute a random sample

Impossible to distinguish between the \( H_0 : \xi - \eta = 0 \) and \( H_A : \xi - \eta \neq 0 \)

Randomisation of the subjects -> Randomisation of the \( u_i \)'s

Tested most powerfully by means of a permutation test

\( T \)-test is a large sample approximation.

(inference is over all possible permutations........)

Roes, Pharmaceutical Statistics 2004, 187-191
Dynamic allocation?

$X_1, X_2, \ldots, X_m$ and $Y_{m+1}, Y_2, \ldots, Y_{m+n}$

$X_i = u_i + V_i, \quad Y_i = u_i + V_i \quad u_i \text{ is associated with the } i\text{-th subject}$

$E(X_i) = u_i + \xi, \quad E(Y_i) = u_i + \eta \quad V_i \text{ with drug & circumstances}$

Allocation to treatment $(u_i)$ in such a way that (you expect, hope):

$\text{Mean}_{1,m}(u_i) = \text{Mean}_{m+1,m+n}(u_i)$

And then, under the Gaussian assumption for $V_i$, the t-test is a (good approximation to) most powerful test.
**Balance, size and power**

**Effect of covariates on size (unadjusted)**

**Effect of covariates and covariate adjustment on precision & bias**


<table>
<thead>
<tr>
<th>Degree of imbalance</th>
<th>STR4</th>
<th>MIN (0.70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p50</td>
<td>p99</td>
</tr>
<tr>
<td>Groups of 50</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Groups of 100</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Groups of 200</td>
<td>6</td>
<td>24</td>
</tr>
</tbody>
</table>

Balance and power

Degree of imbalance in simultaneous distribution
P-values of chi-square test for 3x3 contingency table

<table>
<thead>
<tr>
<th>STR4</th>
<th>MIN (0.70)</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>p1</td>
<td>p1</td>
<td>p1</td>
</tr>
<tr>
<td>p50</td>
<td>p50</td>
<td>p50</td>
</tr>
<tr>
<td>0.22</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>0.87</td>
<td>0.86</td>
<td>0.47</td>
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</tbody>
</table>

Groups of 200

So, interaction between covariates presents a problem.
Balance and power

**Type 1 error & power (survival analysis, 200 pts, 10.000 simul.)**

<table>
<thead>
<tr>
<th></th>
<th>MIN (1.0)</th>
<th>STR2</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₀ (1.0)</td>
<td>Log-rank</td>
<td>0.0352</td>
<td>0.0334</td>
</tr>
<tr>
<td></td>
<td>Stratified Log rank</td>
<td>0.0466</td>
<td>0.0446</td>
</tr>
<tr>
<td>H₁ (1.6)</td>
<td>Log-rank</td>
<td>0.4155</td>
<td>0.4265</td>
</tr>
<tr>
<td></td>
<td>Stratified Log rank</td>
<td>0.4790</td>
<td>0.4904</td>
</tr>
<tr>
<td>H₁ (2.0)</td>
<td>Log-rank</td>
<td>0.7793</td>
<td>0.7852</td>
</tr>
<tr>
<td></td>
<td>Stratified Log rank</td>
<td>0.8215</td>
<td>0.8303</td>
</tr>
</tbody>
</table>
• Prediction of next treatment allocation
  • Small known block sizes in case of stratified randomisation
  • Known variables/parameters of dynamic allocation algorithm

• “Blind” estimation of treatment effect
  • Stratified randomisation:
    • Block size 2 -> bi-modal distribution of pairwise differences
    • Block size 4 -> similar generalization
    • Random lengths of 2 & 4: still possible
  Hence: large block sizes!

Van der Meulen 2006

• Dynamic allocation
  • Similar options (through ancova), but less precise
And now……

• Inference is imperfect….what’s new?

• Principal method may not be the overriding concern, actual implemention could be be (also for more complicated stratified randomisation)

• Advocating transparent account of methods applied (& potential errors) more important & effective.