Dynamic randomization in clinical trials - a review

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Trigger for this presentation

- The ICH support the use of dynamic allocation, and the CONSORT statement declares
  “trials that use minimization are considered methodologically equivalent to randomized trials, even when a randomization element is not incorporated”

- Application of Minimization in clinical trials is still less than 2% of clinical trials. (2011)

- Further education for clinicians regarding dynamic allocation techniques and instruction on their smooth incorporation into clinical studies may be beneficial. - Kimberly Fernandes  Nov 16, 2005
The basics: or the why part

Randomization

- To have valid statistical conclusions
- To eliminate biases that may affect the assessment of the results of the trial
- The distribution of known and unknown factors that may influence patient outcome should be same across the treatment groups.
Broad classification

- **Static**
  - Predefined and unchanged
  - Do not use information on patients that are already in the trial.
  - For small trials with many stratification factors randomization will not insure balance.

- **Dynamic**
  - Not pre-defined
  - Depend on prior patient information
  - Only the first subject’s group assignment is truly chosen at random

Why Dynamic?
- Treatment balance “required” within each level of stratification factors.
Types of Randomization

• Static Randomization
  – Simple Randomization
  – Permuted Block Randomization
  – Stratified Block Randomization

• Dynamic (adaptive) randomization
  – Biased coin randomization - Efron (1971)
    • Urns method
  – The covariate-adaptive algorithms
    • Minimization
      – Tave’s method (1974)
      – Pocock and Simon method (1975)
      – Frane’s method
  – Dynamic balancing randomization (DBR)- Signorini et al
  – Response-adaptive randomization
  – Atkinson’s DA-Optimality method
  – Zelen’s method, minimization urns designs, optimal allocation techniques
Biased coin randomization

• Efron in 1971
• Method for adjustment of assigning probabilities
• Steps:
  – Simple randomization
  – Adjust when the disparity reaches a pre-specified limit.
  – Group with the least subjects will have high probability of assignment.
  – If balance is achieved, the next subject is randomized to any of the groups with equal probability
Urns method - adaptive biased coin approach

- Drawing balls labeled A or B from an urn, with replacement.

- For the first patient, the urn contains $m$ balls of each type (A and B). The first patient is assigned on the basis of a random draw.

- If the assigned treatment “fails,” a ball of the other type is added to the urn. The next patient therefore has a higher probability of receiving the other treatment.

- If the assigned treatment “succeeds,” a ball of the same type is added to the urn. Thus, the next patient has a higher probability of receiving the same treatment.
Urns method - adaptive biased coin approach

• The most widely studied member of the family of adaptive biased-coin designs

• Less affected by selection bias vs permuted-block randomization methods

• Compromise between designs that yield perfect balance in treatment assignments and complete randomization which eliminates experimental bias.

• Forces a small-sized trial to be balanced and approaches complete randomization as the size of the trial (n) increases.
Minimization (Covariate-adaptive randomization)

- Taves and by Pocock & Simon

- A balance function that is minimized by assigning the new patient to a certain treatment.

- Imbalance score is computed based on characteristics, treatment assignment of current and enrolled patients. The patient is assigned to the treatment with the lowest imbalance score.

- Stratification considers the combinations of factor levels as mutually exclusive groups whereas minimization considers important prognostic factors together

- Minimization could be complete or partial.
Example: Minimization

- In a trial of chemotherapy for breast cancer, with stratification factors of clinic site, estrogen receptor status (ER+ or ER-) and menopausal status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trt A</th>
<th>Trt B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Site 2</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>ER+</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>ER-</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

- Patient no: 35 = Site 2, ER+, Post-menopausal
- Subtotal for Trt A: 10+5+9 = 24; Subtotal for Trt B: 9+6+8 = 23
- So allocate to Trt B
Tave’s method

<table>
<thead>
<tr>
<th>Control group</th>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Marginal total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>Underweight</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Marginal total</td>
<td></td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Marginal total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>Underweight</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Marginal total</td>
<td></td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

- 10th subject = male and underweight,
Pocock and Simon method

- Temporarily assign to the control group,
  - Marginal totals of 3 for male and 2 for underweight category;
- Calculate the absolute difference between control and treatment
  - (males: 3 control - 3 treatment = 0; underweight: 2 control - 2 treatment = 0) and sum (0 + 0 = 0);
- Temporarily assign to the treatment group
  - so marginal totals of 4 for male and 3 for underweight category;
- Repeat step 2:
  - (males: 2 control - 4 treatment = 2; underweight: 1 control - 3 treatment = 2) and sum (2 + 2 = 4);
- Assign the 10th subject to the control group because of the lowest sum of absolute differences (0 < 4).

- Also suggested using a variance approach. this approach calculates the variance among treatment groups.
Frane’s method

• Use $P$ values to identify imbalance among treatment groups: a smaller $P$ value represents more imbalance among treatment groups.

• Steps
  – Temporarily assign the subject to both the control and treatment groups;
  – Calculating $P$ values for each of the covariates using a $t$ test or Chi-square test
  – Determine the minimum $P$ value for each control or treatment group
  – Assigning the subject to the group with the larger minimum $P$ value

• The higher minimum $P$ value ($1.0 > 0.317$), indicates better balance is the control group

• Controls quantitative covariates in addition to categorical ones
Dynamic balancing randomization

- Proposed by Signorini et al

- Tree-based method allowing different levels of imbalance in different strata which ensures a balance for each level of prognostic risk factors (conditional balance) whilst at the same time preserving randomness.

- Eg: 2 strata 2 levels; Gender, age groups in the order. DBR attempts to check treatment imbalance within gender first and then age groups and then the overall.

- No guarantee that balance will be achieved across the different levels for each stratum (marginal)
Response-adaptive randomization

• also known as outcome-adaptive randomization

• Advantage of assigning fewer patients to inferior treatment

• More ethical

• Balancing is a concern again.
Measures of performance to provide comparisons between the approaches

• A loss function-
  – interpreted as squared norm of the imbalance vector.
  – A global imbalance measure

• A forcing index- conveys the degree of randomness.
Implementation Challenges

Three types of errors:

– Errors by investigators;
  • Patient classified to wrong strata
  • Incorrect treatment administered (assigns wrong kit or incorrect treatment admin)

– Errors in the algorithm;
  • Algorithm is not tested using simulations

– Errors caused by a faulty drug supply method.
  • Inadequate supply of study drug at site.
  • Not all study drugs are available at site
Conclusion

- The decision about which method to use for allocating patients should be given as much consideration as other aspects of a clinical trial. Appropriately choosing between methods can affect the statistical tests required and what inferences are possible, while affecting the trial credibility. - G.R Pond 2011 May 24, British Journal of cancer,

- Minimization should be the method of choice in assigning subjects in all clinical trials. - Taves DR, 2010 -Contemp Clin Trials, 2010 Mar 31(2):180-4