STATISTICAL CONSIDERATIONS FOR
SEQUENTIAL, MULTIPLE ASSIGNMENT,
RANDOMIZED (SMART) TRIALS

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Outline

- Introduction
- SMART Framework
- Design Elements
- Power and Sample Size
- Example
- Simulation Results
- Conclusions
Goal: Compare adaptive treatment interventions, in which intermediate outcomes guide subsequent treatment decisions for individual patients

Notation:
- X - First stage treatment indicator (0,1)
- R - Tailoring variable result indicator (0,1)
- Z - Second stage treatment indicator (0,1)
SMART Framework

Adaptive Treatment Interventions:

(1,1): First Stage X=0; Second Stage Z=0 for R=0 and R=1
(2,1): First Stage X=1; Second Stage Z=0 for R=0 and R=1
(2,2): First Stage X=1; Second Stage Z=0 for R=0 and Z=1 for R=1
SMART Framework

- An individual patient can be consistent with more than one adaptive regimen
- Patients part of $Z=1$ of the third adaptive intervention are under-represented and bias intent-to-treat comparisons between the adaptive interventions
- Restricted re-randomization
Design Elements

- Randomization Ratios
Randomization Ratios

- Allow for different choice of randomization probabilities in both first and second stage treatment assignments
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Weights
Design Elements

- Randomization Ratios
  - Allow for different choice of randomization probabilities in both first and second stage treatment assignments

- Weights
  - Account for the restricted re-randomization
### Design Elements

- **Randomization Ratios**
  - Allow for different choice of randomization probabilities in both first and second stage treatment assignments

- **Weights**
  - Account for the restricted re-randomization
  - Inverse of the randomization probabilities, across all stages
Design Elements

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- **Piece-wise hazard rates**
Design Elements

- **Randomization Ratios**
  - Allow for different choice of randomization probabilities in both first and second stage treatment assignments

- **Weights**
  - Account for the restricted re-randomization
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- **Piece-wise hazard rates**
  - Partition assumed hazard rate into two intervals: prior to the intermediate assessment, and after the intermediate assessment
Power and Sample Size

Power via Simulation

- Time-to-event distributions of adaptive treatment interventions are compared using a weighted robust score test.
- If test is in favor of adaptive treatment interventions of interest and the one-sided p-value from robust score test $\leq 0.025$, superiority is claimed.
- Repeated 10000 times for each comparison.
- Power is the number of times superiority was achieved, out of the 10000 simulations.
SMART Example

Previously published a SMART to identify an optimal treatment strategy in older patients with chronic lymphocytic leukemia (CLL)*.

First stage randomization 1:1, Second stage randomization 1:1
MRD- CR, IO: 10%, MRD- CR, IVO: 50%

Hazard Rate

<table>
<thead>
<tr>
<th></th>
<th>IO</th>
<th>IO with IM</th>
<th>IO with IM</th>
<th>IVO</th>
<th>IVO with IM</th>
<th>IVO with IM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not MRD-CR</td>
<td>MRD-CR</td>
<td></td>
<td>Not MRD-CR</td>
<td>MRD-CR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.071</td>
<td>0.075</td>
<td>0.050</td>
<td>0.039</td>
<td>0.0375</td>
<td>0.025</td>
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</table>

*Ruppert et al (2019)*
Impact

- **Randomization Ratios**

<table>
<thead>
<tr>
<th>First Stage Randomization</th>
<th>1:1</th>
<th>1:1</th>
<th>1:1</th>
<th>1:2</th>
<th>1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Stage Randomization</td>
<td>1:1</td>
<td>1:2</td>
<td>1:3</td>
<td>1:1</td>
<td>1:2</td>
</tr>
<tr>
<td>Power</td>
<td>0.843</td>
<td>0.803</td>
<td>0.780</td>
<td>0.553</td>
<td>0.479</td>
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</tbody>
</table>

- **Weights**

<table>
<thead>
<tr>
<th>1st Stage</th>
<th>2nd Stage</th>
<th>Consider 1st stage?</th>
<th>SE</th>
<th>Robust SE</th>
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<tbody>
<tr>
<td>1:1</td>
<td>1:1</td>
<td>N</td>
<td>0.1788</td>
<td>0.2001</td>
</tr>
<tr>
<td>1:1</td>
<td>1:1</td>
<td>Y</td>
<td>0.1264</td>
<td>0.2001</td>
</tr>
<tr>
<td>1:1</td>
<td>1:2</td>
<td>N</td>
<td>0.1654</td>
<td>0.1771</td>
</tr>
<tr>
<td>1:1</td>
<td>1:2</td>
<td>Y</td>
<td>0.1169</td>
<td>0.1771</td>
</tr>
<tr>
<td>1:2</td>
<td>1:1</td>
<td>N</td>
<td>0.1619</td>
<td>0.1742</td>
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<tr>
<td>1:2</td>
<td>1:1</td>
<td>Y</td>
<td>0.1156</td>
<td>0.1839</td>
</tr>
</tbody>
</table>
Conclusions

- SMART designs allow to estimate not only can stage-specific treatment effects, but also sequential treatment effects.
- Overview of design considerations show flexibility and usefulness of a SMART.
- R code available and RShiny app on the way.
SMART Design Bin/TTE Simulations

Design
- Sample Size
- Power

Hazard Rate Assumption
- Constant
- Piecewise

Type I Error
0.05

Beta
0.2

Time of New Interval (Years)
1

1st Stage Randomization: Treatment 1
0.5

2nd Stage Randomization: Treatment 1
0.5

Minimum Censoring Time
0.5

Maximum Censoring Time
0.5

Treatment 1

Overall HR1
1

HR for non-responders
0.8

Response time for responders
0.8

Post-response HR for Treatment 1
0.9
Thank you

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Appendix: Piece-wise Hazard Rate Data Generation

- **Piece-wise Hazard Rate assumption**
  - Partition assumed hazard rate into two intervals: prior to the intermediate assessment, and after the intermediate assessment

- **Data Generation:**
  - Generate event times from an exponential distribution with respective overall group hazard rates
  - Intermediate assessment is conducted
  - Patients whose event times are less than the time of the intermediate assessment are considered non-responders
  - Of the patients who make it to the intermediate assessment, proportions of those who will be responders or non-responders will be split based on hypothesized response rates
  - Generate new event times for each group based on hypothesized increased or decreased in hazard rate