Sequential, Multiple Assignment, Randomized Trials (SMART)

Module 2
Outline

• Why SMART Experimental Designs?
• What is a SMART?
• SMART Design Principles
• Sample Size Considerations
• SMART vs. Other Experimental Designs
Should I consider a SMART?

Do I want to develop an Adaptive Intervention? 
Yes → Are there open questions preventing the construction of an effective AI? 
Yes → Are there open questions at multiple decision points within an AI? 
Yes → SMART

No → No → No → Consider another study design
Scientific Questions

Example scientific questions:

- How long should we offer the first treatment?
- What tactic should we use for non-responders to the intervention?
- What tactic should we use for responders to the intervention?
- How to re-engage participants who are non-adherent or drop-out?
- What is the most effective delivery location for the intervention?
- What is the most effective delivery mode for the intervention?
- What is the best way to define non-response?
Outline

• Why SMART Experimental Designs?
• **What is a SMART?**
• SMART Design Principles
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• SMART vs. Other Experimental Designs
What is a SMART?

A multi-stage randomized trial

- Each stage corresponds to a scientific question(s) concerning the selection and adaptation of intervention options.
- A randomization takes place at each decision point of scientific interest.
- Some (or all) participants are randomized more than once
  - Randomizations may depend on outcomes of prior treatment.

The goal of a SMART is to inform the construction of an Adaptive Intervention.
AIM-ASD SMART
(N = 192; R01-HD073975; PI: Kasari)

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

DTT

DTT + Parent Training

DTT

DTT + JASP + EMT

JASP + EMT + Parent Tng

JASP + EMT

JASP + EMT

DTT + JASP + EMT

Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

Week 16

a

b

c

d

e

f

g

h
Should I consider a SMART?

Do I want to develop an Adaptive Intervention?  Yes  No

Are there open questions preventing the development of an effective AI?  Yes  No

Are there open questions at multiple decision points within an AI?  Yes  No

Consider another study design
AIM-ASD SMART
(N = 192; R01-HD073975; PI: Kasari)
Would we need a SMART if … we knew what to offer responders?
Would we need a SMART if …
we knew what to offer responders?
Would we need a SMART if … we knew how to begin the intervention sequence?
Would we need a SMART if ... we knew how to begin the intervention?
What is a SMART?

A multi-stage randomized trial

- Each stage corresponds to a (potential) critical decision point in an adaptive interventions.

- A randomization takes place at each decision point of scientific interest.

- Some (or all) participants are randomized more than once
  - Randomizations may depend on outcomes of prior treatment.

The goal of a SMART is to inform the construction of an Adaptive Intervention.
Outline

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SMART Design Considerations

**Keep it Simple**

Should re-randomization be restricted?

- Restricted = in the SMART, different intervention options are considered for different subgroups of participants.

- Use well-justified tailoring variables to restrict the randomization(s) based on ethical, scientific and practical considerations.

  - **Ethical**: treatment options are appropriate for this subset of the participants.
  
  - **Scientific**: based on empirical evidence the best treatment for a specific subset of participants is already established.
  
  - **Practical**: e.g., save the more intense/costly (step-up) options for those who need it most.
SMART Design Considerations

{Keep it Simple}
SMART Design Considerations

{Keep it Simple}

Focus on a few scientific aims that will further the development of a high-quality adaptive intervention

- Select a **primary aim**: Sample Size is based on this aim
- Select **secondary aims**: Use additional data that could be used to further inform the development of an adaptive intervention.
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
- Compare second-stage options among slow-responders
- Compare embedded adaptive interventions
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
- Compare second-stage options among slow-responders
- Compare embedded adaptive interventions

**Hypothesis 1:** Starting an AI with JASP+EMT will improve social communication more than starting with DTT.

These are example hypotheses.
SMART Design Considerations

Hypothesis 1: Starting an AI with JASP+EMT will improve social communication more than starting with DTT.

These are example hypotheses.
SMART Design Considerations

<table>
<thead>
<tr>
<th>First-stage intervention</th>
<th>Embedded Tailoring Variable</th>
<th>Second-stage intervention</th>
<th>Experimental Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTT</td>
<td>Responders 50%</td>
<td>DTT</td>
<td>n=25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTT</td>
<td>n=25</td>
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<tr>
<td></td>
<td></td>
<td>DTT+JASP+EMT</td>
<td>n=25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JASP+EMT+Parent Tng</td>
<td>n=30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JASP+EMT</td>
<td>n=30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JASP+EMT+DTT</td>
<td>n=20</td>
</tr>
<tr>
<td>N=200</td>
<td>Responders 60%</td>
<td>Slower Responders</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slower Responders</td>
<td></td>
</tr>
</tbody>
</table>

Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

These is simulated data.
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
- Compare second-stage options among slow-responders
- Compare embedded adaptive interventions

**Hypothesis 2**: Among slow-responders, blending JASP+EMT and DTT will improve social communication more than continue.

These are example hypotheses.
Hypothesis 2: Among slow-responders, blending JASP+EMT and DTT will improve social communication more than continue.

These are example hypotheses.
Hypothesis 2: Among slow-responders, blending JASP+EMT and DTT will improve social communication more than continue.
These are example data.
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
- Compare second-stage options among slow-responders
- Compare embedded adaptive interventions

First, let’s define what we mean by “embedded adaptive interventions”…
Embedded Adaptive Intervention #1

Start with DTT

*Then*, at week 6

*If* response status = responder

*Then*, stage 2 intervention = \{add Parent Training\}

*Else if* response status = slow responder

*Then*, stage 2 intervention = \{Blend with JASP+EMT\}
Embedded Adaptive Intervention #2

First-stage intervention: DTT

Embedded Tailoring Variable:
- Responders
- Slower Responders

Second-stage intervention:
- DTT + Parent Training → a
- DTT → b
- DTT + JASP + EMT → c
- Slower Responders

Experimental Conditions:
- a
- b
- c
- d
- e
- f
- g
- h

Treatment Outset:
- Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

Week 16
Embedded Adaptive Intervention #3

**First-stage intervention**
- DTT
- JASP + EMT

**Embedded Tailoring Variable**
- Responders
- Slower Responders

**Second-stage intervention**
- DTT + Parent Training
- DTT
- DTT + JASP + EMT
- JASP + EMT + Parent Tng
- JASP + EMT
- JASP + EMT + DTT

**Experimental Conditions**
- a
- b
- c
- d
- e
- f
- g
- h

**Treatment Outset**
- Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

**Week 16**
Embedded Adaptive Intervention #4

Start with DTT

Then, at week 6

Stage 2 intervention = {Continue}
Embedded interventions 5, 6, 7, and 8 are similar but begin with JASP+EMT.
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
- Compare second-stage options among slow-responders
- Compare embedded adaptive interventions

**Hypothesis 3:** The AI that begins with JASP+EMT and (a) adds parent training for responders, and (b) blends for slower responders will improve social communication more than the similar AI which begins with DTT.

These are example hypotheses.
Hypothesis 3: The AI that begins with JASP+EMT and (a) adds parent training for responders, and (b) blends for slower responders will improve social communication more than the similar AI which begins with DTT.

These are example hypotheses.
SMART Design Considerations

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

N=200

Responders 50%

DTT

Responders 60%

JASP + EMT

Slower Responders

DTT + Parent Training

DTT

JASP + EMT + Parent Tng

JASP + EMT

JASP + EMT + DTT

Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

Week 16

n=25

n=25

n=30

n=20

These is simulated data.
SMART Design Considerations

Primary Aim 1 Examples

- Compare initial intervention options
  - **H1**: JASP + EMT is better than DTT

- Compare second-stage options among slow-responders
  - **H2**: Blending is better than Continue among slow-responders

- Compare embedded adaptive interventions
  - **H3**: AI#1 is better than AI#5

These are example hypotheses.
SMART Design Considerations

A typical Secondary Aim

- Identify ways to more deeply-tailor the AI

  **H4:** Among early responders, those whose parents demonstrate greater buy-in for the initial treatment will benefit more from parent training than from continue.

Why is this hypothesis useful?

- This hypothesis allows us to test a candidate tailoring variable, buy-in, which might moderate the effect of the stage-2 intervention for slower-responders.
- Testing this hypothesis could lead to more refined tailoring of the adaptive intervention in future iterations.

These are example hypotheses.
SMART Design Considerations

First-stage intervention

- DTT
- JASP + EMT

Embedded Tailoring Variable

- Responders
- Slower Responders

Second-stage intervention

- DTT + Parent Training
- DTT
- DTT + JASP + EMT
- JASP + EMT + Parent Tng
- JASP + EMT
- JASP + EMT + DTT

Experimental Conditions

- a
- b
- c
- d
- e
- f
- g
- h

Treatment Outset

Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

Week 16
SMART Design Considerations

These are example hypotheses.
Example of a More Deeply Tailored AI

Start with DTT

*Then*, at week 6

*If* response status = responder
  
  *Then,*
  
  *If* parent buy-in={high}
    
    *Then*, stage 2 = {add Parent Training}

  *Else, if* parent buy-in={low}
    
    *Then* stage 2 ={add parent training or continue}

*Else if* response status = slow responder
  
  *Then*, stage 2 = {Blend with JASP+EMT}
Example of a More Deeply Tailored AI

Responder with

High Parent Buy-In → Add Parent Training

Low Parent Buy-In → Add Parent Training or Continue

Slow-Responders → JASP+EMT

DTT
Outline

• Why SMART Experimental Designs?
• What is a SMART?
• SMART Design Principles
• Sample Size Considerations
• SMART vs. Other Experimental Designs
Sample Size Considerations for Any Randomized Trial

• The Primary Aim determines the study’s total sample size
  • Often based on a hypothesis test with a Type-I error rate of 5% and ≥80% power
  • Must be pre-planned
  • Must be highly-specific

• Given the study’s total sample size, investigators then provide the power for Secondary Aims as a courtesy
  • May tolerate higher Type-I error and lower power
  • Greater flexibility in level of pre-specification
  • Specificity desired

• SMARTs are no different
**Sample Size**

**H1:** Starting with JASP + EMT is better than starting with DTT

Sample size formula is the same as for a **two group comparison.**

\[ N \geq \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \]

\( \delta \) is the smallest effect size the investigator would like to detect.
**Sample Size**

**H2:** Among slow-responders, Blending is better than Continue

Sample size formula is same as a two group comparison of slow-responders.

\[
N \geq \left( \frac{4(\frac{z_{1-\alpha}}{2} + z_{1-\beta})^2}{\delta^2} \right) / (1 - r)
\]

\( r \) is the probability of response to first-stage treatment
Sample Size

\[ N = \text{sample size for the entire trial} \]

<table>
<thead>
<tr>
<th></th>
<th>H1</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ = .3</td>
<td>( N = 402 )</td>
<td>( N = 402/(1 - r) )</td>
</tr>
<tr>
<td>δ = .5</td>
<td>( N = 146 )</td>
<td>( N = 146/(1 - r) )</td>
</tr>
</tbody>
</table>

\( \alpha = .05 \) (two sided), power = \( 1 - \beta = .85 \), \( r \) = response rate
H3: AI #1 has better outcomes compared to AI #5
H3: AI #1 has better outcomes compared to AI #5

- Sample size formula for the comparison of two AIs that begin with different treatments based on an end of study outcome

\[ N \geq \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \times 2 \]

<table>
<thead>
<tr>
<th>Type I error rate (2-sided)</th>
<th>Power</th>
<th>Standardized Difference</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>80%</td>
<td>0.3</td>
<td>698</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>252</td>
</tr>
</tbody>
</table>
Sample Size

**H3:** AI #1 has better outcomes compared to AI #5

- Sample size formula for the comparison of two AIs that begin with different treatments based on an end of study outcome

- But the sample size formulae differ depending on the type of SMART

- What if only slow responders were re-randomized?
Sample Size: Only Slow Responders Re-Randomized

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<td>DTT</td>
<td>a</td>
</tr>
<tr>
<td>JASP + EMT</td>
<td>Slower responders</td>
<td>DTT + JASP + EMT</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>Responders</td>
<td>JASP + EMT</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>Slower Responders</td>
<td>DTT + JASP + EMT</td>
<td>e</td>
</tr>
</tbody>
</table>

Treatment Onset  
Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement  
Week 16
Sample Size

H3: Comparing two AIs that begin with different treatments

- Based on an end of study outcome

\[
N \geq \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \times (2 - r)
\]

<table>
<thead>
<tr>
<th>Type I error rate (2-sided)</th>
<th>Power</th>
<th>( r )</th>
<th>Standardized Difference</th>
<th>( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>80%</td>
<td>50%</td>
<td>0.3</td>
<td>526</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>191</td>
</tr>
</tbody>
</table>
H3: Comparing two AIs that begin with different treatments

- Everything just presented is based on a continuous end of study outcome
- Sample size formula for various types of outcomes are available:
  - Continuous Outcomes: Oetting, A.I., et al. (2011)
Outline

• Why SMART Experimental Designs?
• What is a SMART?
• SMART Design Principles
• Sample Size Considerations
• **SMART vs. Other Experimental Designs**
SMART vs. Other Experimental Designs

- Randomized Control Trial
- Non-responder Trial
- Enhanced Non-responder Trial
- Multiple, Single-stage Trials
- Factorial Designs
- Crossover
- Adaptive Trials
The primary aim of an RCT is to confirm the effectiveness of the adaptive intervention compared to an alternative intervention.
SMART vs. Non-responder Trial

- JASP+EMT
- Slower Responders
- JASP+EMT
- DTT+JASP+EMT

Point of Slow Response + Week 16
SMART vs. Enhanced Non-responder Trial
SMART vs. Multiple, Single-stage Trials

• An alternative to SMART designs is to use data from multiple, single-stage trials to construct an Adaptive Intervention.
SMART vs. Multiple, Single-stage Trials

Trial 1:
- Randomized trial of initial intervention options
- Choose the best stage 1 option.

Trial 2:
- Randomized trial of secondary intervention options
- Choose the best stage 2 option.
SMART vs. Multiple, Single-stage Trials

There are a number of possible disadvantages to this approach:

- Delayed Intervention Effects
- Adherence/Drop out
- Selection Effects
- Prescriptive Effects
SMARTs are Factorial Experiments

- A factorial experiment is an experimental design with multiple factors where the factors are crossed.

- A SMART is often a special form of a factorial experiment where factors are employed sequentially.

- In SMART, the treatment effects are defined in the context of a sequence of treatments.
A repeated measurements design where patients cross over from one treatment to another during the course of the trial.

Typically the aim in a crossover trial is to evaluate stand-alone treatments, not to address questions concerning AIs.

There is a goal to wash out the carryover effects in a crossover trial, while SMARTs are often motivated by a desire to understand the carryover effects.
SMART vs. Adaptive Trials/Designs

- A clinical trial design that allows adaptations or modifications to aspects of the trial while the study is still ongoing (Chang, 2007)

- Example modifications to the trial include:
  - Stopping the trial early either for success, futility or harm
  - Dropping arms or doses or adjust doses
  - Modifying randomization rate to increase probability of allocation to the most appropriate arm.

- Adaptive Trial Designs use information from a set of participants to change the design for future participants.

- SMART use information from a single participant to decide how to modify the intervention for that particular participant.
Questions?
Design Practicum

Goal: Review critical questions discussed during the design practicum and sketch a design to address these questions.

45 minutes: Small group work to outline the argument / rationale for your proposed design.

30 minutes: Large group discussion -- 2 groups share study design for discussion and feedback.