Getting SMART about Adaptive Interventions: A Conceptual Introduction

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Outline

Adaptive Interventions
  What? Why?
Evaluating versus Building an Adaptive Intervention?
Sequential Multiple Assignment Randomized Trial (SMART)
  What are SMARTs?
SMART Design Principles
  Keep it Simple
  Choosing Primary and Secondary Hypotheses
A (not-so) SMART Alternative
Take Home Points
SMART Case Studies
Today is All About Discussion

To encourage this, we begin with an exercise:

- Given what you already know or have heard about adaptive interventions and SMARTs, please write down your top 2 burning questions.
Adaptive Interventions

(an aside: focus of today is on time-varying adaptive interventions)
Definition: A Adaptive Intervention is

- a sequence of individually tailored decision rules
- that specify whether, how, or when
- and based on which measures
- to alter the dosage (duration, frequency or amount), type, or delivery
- at critical decision points in the course of care.

Adaptive Interventions (AIs) help guide the type of sequential treatment decision making that is typical (and often needed!) of clinical practice.
Concrete Example of an Adaptive Intervention
Child ADHD in Schools, Ages 6-12

- Responder status measured by school-teacher.
- Goal is to min. symptoms / max. school performance.
Concrete Example of an Adaptive Intervention

Child ADHD in Schools, Ages 6-12

What does it look like from researcher’s/clinician’s POV?

What does it look like from the child’s/parent’s POV?
What are the parts of an Adaptive Intervention?

1. Critical decision points: based on time or other measures
2. Treatment options at each stage
3. Tailoring variables: to decide how to adapt treatment
4. Decision rules: inputs tailoring variable, outputs treatments

aka: dynamic treatment regimens, adaptive txt strategies, txt algorithms, medication algorithms, stepped care, txt policies, multi-stage strategies...
Why Adaptive Interventions?

Necessary...

- Nature of chronic disorders/phenomena (substance use, mental health, autism, diabetes, cancer, HIV/AIDS)
  - Waxing and waning course (multiple relapse, recurrence)
  - Life events, comorbidities, non-adherence may arise
- Disorders for which there is no widely effective treatment.
- Disorders for which there are widely effective treatments, but they are costly or burdensome.

**Bottom line**: High heterogeneity in response to treatment
  - Within person (over time) and between person

All require sequences of treatment decisions!
Ok, so adaptive interventions are great, but... 
...there are so many unanswered questions.

Next, we’ll talk research...but first...
Questions and Discussion about Adaptive Interventions
GENERATING HYPOTHESES vs BUILDING vs EVALUATING ADAPTIVE INTERVENTIONS?
3 Different Research Questions/Aims
⇒ 3 Different Research Designs

► **Aim Type 1**: When generating hypotheses about an Adaptive Intervention

► **Aim Type 2**: When building an Adaptive Intervention

► **Aim Type 3**: When evaluating a particular Adaptive Intervention
3 Different Research Questions/Aims

⇒ 3 Different Research Designs

Some example questions:

- **Aim Type 1 (Hypothesis Gen.) Example**: Does augmenting txt for non-responders (as observed in a previous trial) correlate with better outcomes?

- **Aim Type 2 (Building) Example**: What are the best tailoring variables or decision rules?

- **Aim Type 3 (Evaluating) Example**: Does an adaptive intervention have a statistically and clinically signif. effect as compared to control intervention?
3 Different Research Questions/Aims
⇒ 3 Different Research Designs

- **Aim Type 1:** When generating hypotheses about an Adaptive Intervention
- **Aim Type 2:** When building an Adaptive Intervention
- **Aim Type 3:** When evaluating a particular Adaptive Intervention

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<td>YES</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Building</td>
<td>≈</td>
<td>YES</td>
</tr>
<tr>
<td>3</td>
<td>Evaluating</td>
<td></td>
<td>≈</td>
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e.g., analysis of previous RCT
SMART
RCT
Questions and Discussion about the Three Types of Aims

(we will loop back to this idea near the end of the Taste)
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIALS (SMARTs)
What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- Multi-stage trials; same participants throughout
- Each stage corresponds to a critical decision point
- At each stage, subjects randomized to set of treatment options
- **The goal of a SMART is to inform the development of adaptive interventions.**

I will give you an example SMART, but first...
Background for an Example SMART

ADHD Treatment in Children Ages 6-12

- Both medication (MED) and behavioral modification (BMOD) have been shown to be efficacious
- However, there is much debate on whether first-line intervention should be pharmacological or behavioral, especially in younger children
- Further, there is a need for a ”rescue treatment” if the first treatment does not go well because 20-50% of children do not substantially improve on BMOD or MED
- So important questions for clinical practice include “What treatment do we begin with: BMOD or MED?” ”Among non-responders, what second treatment is best?”
Concrete Example of a SMART: Child ADHD

PI: William Pelham, PhD, Florida International University, **IES-Funded Grant**

N = 153, 8 month study, Monthly non-response (*ITB* < 75% and *IRS* > 1 domain)

**Diagram Description:**
- MED: Responders → MED
- Non-Responders → R
- R: Responders → Continue: MED
  - Intensify: Higher Dose MED
  - Augment: MED + BMOD
- Non-Responders → R
  - Continue: BMOD
  - Intensify: Increase BMOD
  - Augment: MED + BMOD
One of Four Adaptive Interventions Within the SMART
4 Embedded Adaptive Interventions in this SMART
Questions and Discussion about SMARTs

(next, we will dive in deeper and discuss SMART design principles)
SMART DESIGN PRINCIPLES
SMART Design Principles

- KISS Principle: Keep It Simple, Straightforward
- Power for simple important primary hypotheses
- Take Appropriate steps to develop a more deeply-individualized (optimized) Adaptive Intervention
Keep It Simple, Straightforward

Overarching Principle

At each stage, or critical decision point,…

- Restrict class of treatment options only by ethical, feasibility, or strong scientific considerations

- If you do restrict randomizations, use low dimensional summary to restrict subsequent treatments
  - Use binary responder status
  - Should be easy to use in actual clinical practice

- Collect additional, auxiliary time-varying measures
  - To develop a more deeply-tailored Adaptive Intervention
  - Think time-varying effect moderators
SMART Design: Primary Aims

Choose a simple primary aim/question that aids development of an adaptive intervention.

Statistical methods used here aim to reduce uncertainty so the investigator can come away with a solid answer.

Sample size for the SMART chosen based on the hypothesis test associated with this aim (e.g., use standard $\alpha = 5\%$).
Primary Aim Example 1
What is the effect of starting with BMOD vs MED on longitudinal outcomes?

<table>
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<tr>
<th>ES</th>
<th>N</th>
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<tbody>
<tr>
<td>0.8</td>
<td>34</td>
</tr>
<tr>
<td>0.5</td>
<td>83</td>
</tr>
<tr>
<td>0.2</td>
<td>505</td>
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\[ \rho = 0.60 \]
\[ \alpha = 0.05 \]
\[ \beta = 0.20 \]
SMART Design: Secondary Aims

Choose **secondary aims/questions** that further develop the Adaptive Intervention and take advantage of sequential randomization to eliminate confounding.

Statistical methods used here aim to generate hypotheses, e.g., generate good hypotheses about additional tailoring variables or moderators.

Here, investigators will tolerate hypothesis tests with higher Type-I error, e.g., $\alpha = 10\%$. 

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**SMART Case Studies**

**Keep it Simple**

Choosing Primary and Secondary Hypotheses
Secondary Aim Example 1
Among non-responders, is it better to INTENSIFY vs AUGMENT? On various occasions, I have seen this be the Primary Aim.
Secondary Aim Example 2
Is there a difference between two of the embedded adaptive interventions? This could also be a Primary Aim.

Secondary Aim Example 3

Build a more deeply tailored adaptive intervention (go beyond the 4 embedded adaptive interventions). Rarely, would this be a Primary Aim.

X1 = demographics, genetics, sub-diagnoses, co-morbidities, etc...

X2 = adherence, time to NR, allegiance with therapist/psychiatrist
Questions and Discussion about Sequential Multiple Assignment Randomized Trials (SMARTs)
A (potentially not-so) SMART Alternative
Back to the idea of generating hypotheses vs building vs evaluating adaptive interventions...

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Why not use multiple RCTs to build an adaptive intervention?
Concrete Example of a SMART: Child ADHD
PI: William Pelham, PhD, Florida International University, IES-Funded Grant
N = 153, 8 month study, Monthly non-response (ITB < 75% and IRS > 1 domain)
Why Not Use Multiple RCTs to Construct an AI?

Three Concerns about Using Multiple Trials as an Alternative to a SMART

1. Concern 1: Delayed Therapeutic Effects
2. Concern 2: Diagnostic Effects
3. Concern 3: Cohort (Sample Selection) Effects

All three concerns emanate from the basic idea that constructing an adaptive intervention based on a "local" study-to-study point of view may not be optimal.
TAKE HOME POINTS
Take Home the Following

- Adaptive Interventions individualize treatment up-front and throughout; they are guides for clinical practice

- SMARTs are used to **build** better Adaptive Interventions
  - Next study: RCT of SMART-optimized AI vs control

- SMARTs are not adaptive trial designs (confusing!)

- SMARTs do not have to be complicated

- SMARTs do not necessarily require larger sample sizes
SMART CASE STUDIES

(the most flavorful part of the Taste!)
Autism SMART \((N = 61)\)

PI: Kasari (UCLA). (ages 5-8; planned \(N = 98\) but recruitment difficult, despite multi-site. Wk12 response rates much higher than anticipated.)
Longitudinal Analysis of the Autism SMART

\[ Y_t = \text{Socially communicative utterances over 36 weeks} \]

<table>
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<tr>
<th>AI</th>
<th>Estimate</th>
<th>95% CI</th>
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<tr>
<td>(AAC, AAC+)</td>
<td>51.4</td>
<td>[45.6, 57.3]</td>
</tr>
<tr>
<td>(JASP, AAC)</td>
<td>40.7</td>
<td>[34.5, 46.8]</td>
</tr>
<tr>
<td>(JASP, JASP+)</td>
<td>39.3</td>
<td>[32.6, 46.0]</td>
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Child ADHD SMART
 PI: William Pelham, PhD, Florida International University
 $N = 153$, 8 month study, Monthly non-response ($ITB < 75\%$ and $IRS > 1$ domain)
Longitudinal Analysis of the ADHD SMART

\[ Y_t = \text{Classroom performance over 8 months (school year)} \]
Interventions for Minimally Verbal Children with Autism
PI: Kasari(UCLA), Kaiser(Vanderbilt), Smith(Rochester), Lord(Cornell), Almirall(Mich)

JASP (joint attention and social play)
- Non-Responders (Parent training no feasible)
- Responders (Blended txt unnecessary)
  - JASP + DTT
  - Continue JASP
  - JASP + Parent Training

DTT (discrete trials training)
- Non-Responders (Parent training not feasible)
- Responders (Blended txt unnecessary)
  - JASP + DTT
  - Continue DTT
  - DTT + Parent Training
Interventions for Minimally Verbal Children with Autism

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- **JASP** (joint attention and social play)
  - Non-Responders (Parent training not feasible)
    - Continue JASP
  - Responders (Blended txt unnecessary)
    - **JASP + DTT**
      - Continue JASP
    - **JASP + Parent Training**
      - Continue JASP
  - **R**

- **DTT** (discrete trials training)
  - Non-Responders (Parent training not feasible)
    - Continue DTT
  - Responders (Blended txt unnecessary)
    - **DTT + Parent Training**
Adaptive Implementation Intervention in Mental Health
PI: Kilbourne; Co-I: Almirall (Aim is to improve the uptake of a psychosocial intervention for mood disorders)

60 (75% of) community-based outpatient clinics (sites) that have not responded to 6mo of REP

Augment for 6mo: REP + EF

Responder Sites

Continued Non-Responding Sites

Discontinue

Continue 6mo: REP + EF

Augment 6mo: REP + EF + IF

Responder Sites

Discontinue

Continue 6mo: REP + EF + IF

Continued Non-Responding Sites
Early Trigger for NR: 2+ HDD

Late Trigger for NR: 5+ HDD

8 Week Response

Non-Response

Early Trigger for NR: 2+ HDD

Late Trigger for NR: 5+ HDD

8 Week Response

Non-Response

R

R

R

R

R

R

Non-Response

Non-Response

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone
Questions and Discussion about SMART Case Studies
Thank you! Questions?

Email me with questions about this presentation:
  ▶ Daniel Almirall: dalmiral@umich.edu

Find papers on SMART:
  ▶ http://www.lsa.stat.umich.edu/~samurphy/ (Susan Murphy)
  ▶ http://methcenter.psu.edu (Linda Collins)

More papers and these slides on my website (Daniel Almirall):
  ▶ http://www-personal.umich.edu/~dalmiral/