Experiences with a Novel Clinical Trial Design
Developing Dynamic, Sequential Treatments that Optimize Mental Health Outcomes

Introduction to Adaptive Interventions and SMART Designs
2:45-3:10PM, Daniel Almirall and Susan Murphy, UMich

SMART Studies for Alcohol and Cocaine Dependence
3:15-3:40PM, James McKay, UPenn

Adaptive Treatments for Children with ADHD
3:45-4:10PM, William E. Pelham, FIU

Testing Variants of Treatments for Substance Use Disorders During Pregnancy
4:30-4:55PM, Hendree Jones, RTI

Innovative Communication Intervention for Older Nonverbal Children with Autism
5:00-5:25PM, Connie Kasari, UCLA
Introduction to Adaptive Interventions and SMART Study Design Principles

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None
Outline

Adaptive Interventions
  What? Why?
  Adaptive Intervention Development Considerations

Sequential Multiple Assignment Randomized Trial (SMART)
  What are SMARTs?

SMART Design Principles
  Keep it Simple
  Choosing Primary and Secondary Hypotheses

Discussion
Definition of an Adaptive Intervention

An adaptive intervention (AI) is a sequence of individually tailored decision rules that specify whether, how, and when to alter the intensity, type, dosage, or delivery of treatment at critical decision points in the medical care process.

Adaptive Interventions operationalize sequential decision making with the aim of improving clinical practice.

aka: dynamic treatment regimes, adaptive treatment strategies, treatment algorithms, structured treatment interruptions, ...
Concrete Example of Adaptive Intervention

Pediatric Anxiety Example (SAD, GAD, SoP)

- **Goal is to minimize the child’s symptom profile/trajectory.**

**First-line Txt**
- **Responder**
- **Non-Responders**

**Tailoring Variable**

**Second-line Txt**
- **Maintain:** CBT
- **Add Treatment:** CBT + MED

**Adaptive Intervention Development Considerations**

**SMART Design Principles**

**What? Why?**

**Sequential Multiple Assignment Randomized Trial (SMART)**

**Adaptive Interventions**

**Experimental Designs for Developing Adaptive Interventions**
What makes up an Adaptive Intervention?

- **CBT**
- Responder
- Non-Responders

**Tailoring Variable**

- Maintain: CBT
- Add Treatment: CBT + MED
Why Adaptive Interventions?

Necessary because...

- The chronic nature of mental health disorders
  - Waxing and waning course (multiple relapse, recurrence)
  - Genetic and non-genetic factors influence course
  - Co-occurring disorders may arise

- High patient heterogeneity in response to treatment
  - Within person (over time) differential response to treatment
  - Between person differential response to treatment

- More is not always better!
Why Adaptive Interventions?
Can be used to inform how to best...

- Adapt treatment to a patient’s chronic/changing course
- Deliver appropriate treatment when needed most
- React to non-adherence or side-effect profiles
- Reduce treatment burden; only what is necessary
- Deliver early treatments with positive downstream effects
- Sift through available treatment options
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⇒ More personalized care, over time
⇒ Improving clinical practice
Developing an Adaptive Intervention

- For who are we developing the adaptive strategy? Population, or Context, question.
- What is the goal of the adaptive intervention? Objectives question.
- What is the optimal sequencing of treatments? Sequencing question.
- When do we switch, augment, or maintain treatment? Timing question.
- Based on what information do we make decisions? Tailoring question.
What is a tailoring variable?
A time-varying measure that prescribes one treatment at one level and another treatment at another level.

Among responders to combination CBT + MED:
- More adherence to CBT
- More adherence to MED
- Step Down to CBT Only
- Maintain CBT+MED

**Mean Anxiety Score**

**Adherence to medication relative to CBT**
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 are randomized to a set of treatment options
- Treatment options at randomization may be restricted depending on intermediate outcome/treatment history
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 are randomized to a set of treatment options
- Treatment options at randomization may be restricted depending on intermediate outcome/treatment history
- The goal of a SMART is to inform the development of adaptive intervention strategies.
Concrete Example of a SMART: Pediatric Anxiety

Add Treatment: CBT + MED + FT  Non-Responders
CBT + MED Maintain: CBT + MED
Step Down: CBT Only
Responders
Non-Responders
O1 ——— First-line Txt ——— O2 + Primary Tailoring Variable ——— Second-line Txt ——— Y
CBT + MED
CBT
Add Treatment: CBT + MED
Switch Treatment: MED
Maintain: CBT + MED
Step Down: CBT Only
Maintain: CBT
Add Treatment: CBT + MED
Responders
Responders
Non-Responders
One Adaptive Intervention Within the SMART

Add Treatment: CBT + MED + FT
Non-Responders

Maintain: CBT + MED
Responders

Step Down: CBT Only
Non-Responders

Maintain: CBT
Responders

Add Treatment: CBT + MED
Non-Responders

Switch Treatment: MED
Responders

CBT

O1 ——— First-line Txt ——— O2 + Primary Tailoring Variable ——— Second-line Txt ——— Y
Another Adaptive Intervention Within the SMART

CBT + MED

Non-Responders

Responders

CBT

Non-Responders

Responder

Add Treatment: CBT + MED + FT
Maintain: CBT + MED
Step Down: CBT Only
Maintain: CBT
Add Treatment: CBT + MED
Switch Treatment: MED

O₁ ——— First-line Txt
O₂ + Primary Tailoring Variable
Second-line Txt ——— Y
4 Embedded Adaptive Interventions in this SMART

AIS 1
- **CBT + MED**
  - Non-Responders ➔ **Add Treatment:** CBT + MED + FT
  - Responders ➔ **Step Down:** CBT Boost

AIS 2
- **CBT + MED**
  - Non-Responders ➔ **Add Treatment:** CBT + MED + FT
  - Responders ➔ **Maintain:** CBT + MED

AIS 3
- **CBT**
  - Responders ➔ **Maintain:** CBT Boost
  - Non-Responders ➔ **Add Treatment:** CBT + MED

AIS 4
- **CBT**
  - Responders ➔ **Maintain:** CBT Boost
  - Non-Responders ➔ **Switch Treatment:** MED
SMART Design Principles

- KISS Principle: Keep It Simple, Straightforward
- Power for Simple Important Primary Hypotheses
- Take Appropriate Steps to Develop an Optimal Adaptive Intervention
Keep It Simple, Straightforward

Overarching Principle

At each stage, or critical decision point,...

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

▶ 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.

Power the SMART to test this hypothesis.
Primary Aim Example 1
What is the main effect of first-line treatment? End of study outcome (e.g., ANOVA).

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| α   | 0.05 |
|β   | 0.20 |

CBT + MED

Non-Responders

Responders

Add Treatment: CBT + MED + FT

Maintain: CBT + MED

Step Down: CBT Only

R

CBT

Add Treatment: CBT + MED

Switch Treatment: MED

O1 - First-line Txt

O2 + Primary Tailoring Variable

Second-line Txt - Y
Primary Aim Example 1

What is the main effect of first-line treatment? Longitudinal outcome (e.g., LMM).

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\[\rho = 0.60\]
\[\alpha = 0.05\]
\[\beta = 0.20\]
Primary Aim Example 2
Identify the best of the 4 embedded adaptive intervention strategies.

AIS 1

CBT + MED

Non-Responders → Add Treatment: CBT + MED + FT

Responders → Step Down: CBT Boost

AIS 2

CBT + MED

Non-Responders → Add Treatment: CBT + MED + FT

Responders → Maintain: CBT + MED

AIS 3

CBT

Responders → Maintain: CBT Boost

Non-Responders → Add Treatment: CBT + MED

AIS 4

CBT

Responders → Maintain: CBT Boost

Non-Responders → Switch Treatment: MED

<table>
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$\pi = 0.85$
SMART Design: Secondary Aims

Choose *secondary aims/questions* that further develop the Adaptive Intervention and take advantage of sequential randomization to eliminate confounding.
Secondary Aim Example 1
Second-line treatment tailoring aim.

First-line Txt  ___________ O2 + Primary Tailoring Variable  ___________ Second-line Txt  —— Y

CBT

→ Non-Responders

O2 = CBT adherence, time to non-response, allegiance with therapist, changes in home environment

Add Treatment: CBT + MED

Switch Treatment: MED

Almirall, Compton, Murphy
Secondary Aim Example 2
Build a more deeply tailored adaptive intervention.

O1 = demographics, genetics, sub-diagnoses, co-morbidities, etc...

O2 = adherence, time to NR, changes at home, etc...

Add Treatment: CBT + MED + FT
Non-Responders

Maintain: CBT + MED
 Responders

Step Down: CBT Only
Non-Responders

Maintain: CBT
 Responders

Add Treatment: CBT + MED
Non-Responders

Switch Treatment: MED
Responders

O2 + Primary Tailoring Variable

First-line Txt
Y
Messages and Misconceptions

- Adaptive Intervention? vs SMART? vs Adaptive Trial?
  - “Adaptive Trial” has other meanings in trials literature
  - In SMART, same patients participate in multiple stages

- SMARTs do not necessarily require larger sample sizes

- SMARTs can be seen as developmental trials
  - Next trial will compare the SMART-optimized Adaptive Intervention versus usual care or other state-of-the-art treatment
Thank you! Questions?

Email me with questions about this presentation:
➤ dalmiral@umich.edu

These slides will be posted on my website:
➤ http://www-personal.umich.edu/~dalmiral/
Extra Slides
Adaptive Treatment for Children with ADHD
B. Pelham, Florida International University

Medication
- Responders
  - Continue Medication
  - Increase Medication Dose
  - Add Behavioral Intervention
- Non-Responders
  - Responders
  - Non-Responders
  - Continue Behavioral Intervention
  - Increase Behavioral Intervention
  - Add Medication
Early Trigger for NR: 2+ HDD

Late Trigger for NR: 5+ HDD

Non-Response

8 Week Response

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Non-Response
Other Alternatives

- Piecing Together Results from Multiple Trials
  - Choose best first-line treatment on the basis of a two-arm RCT; then choose best second-line treatment on the basis of another separate, two-arm RCT
  - Concerns: delayed therapeutic effects, and cohort effects

- Observational (Non-experimental) Comparisons of AIs
  - Using data from longitudinal randomized trials
  - May yield results that inform a SMART proposal
  - Understand current treatment sequencing practices
  - Typical problems associated with observational studies

- Expert Opinion
Why Not Use Multiple Trials to Construct an AI

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

1. Concern 1: Delayed Therapeutic Effect
2. Concern 2: Diagnostic Effects
3. Concern 3: Cohort Effects

All three concerns emanate from the basic idea that constructing an adaptive intervention based on a myopic, local, study-to-study point of view may not be optimal.
Why Not Use Multiple Trials to Construct an AI

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Positive Synergy Btwn First- and Second-line Treatments

Tapering off medication after 12 weeks of use may not appear best initially, but may have enhanced long term effectiveness when followed by a particular augmentation, switch, or maintenance strategy.

Tapering off medication after 12 weeks may set the child up for better success with any one of the second-line treatments.
Why Not Use Multiple Trials to Construct an AI

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Negative Synergy Btwn First- and Second-line Treatments

Keeping the child on medication an additional 12 weeks may produce a higher proportion of responders at first, but may also result in side effects that reduce the variety of subsequent treatments available if s/he relapses.

The burden associated with continuing medication an additional 12 weeks may be so high that non-responders will not adhere to second-line treatments.
Why Not Use Multiple Trials to Construct an AI

Concern 2: Diagnostic Effects

Tapering off medication after 12 weeks initial use may not produce a higher proportion of responders at first, but may elicit symptoms that allow you to better match subsequent treatment to the child.

The improved matching (personalizing) on subsequent treatments may result in a better response overall as compared to any sequence of treatments that offered an additional 12 weeks of medication after the initial 12 weeks.
Why Not Use Multiple Trials to Construct an AI

Concern 3: Cohort Effects

- Children enrolled in the initial and secondary trials may be different.
- Children who remain in the trial(s) may be different.
- Characteristics of adherent children may differ from study to study.
- Children that know they are undergoing adaptive intervention strategies may have different adherence patterns.

**Bottom line:** The population of children we are making inferences about may simply be different from study-to-study.
SMART Design Principles
Choose a Longitudinal Response Measure

Why choose a longitudinal outcome, or a with-in person summary of outcomes over time?

- These are chronic disorders (e.g., child-hood onset anxiety disorder)
- Outcome should incorporate time to initial response as a component
- Quick initial relief of symptoms should be valued