Getting SMART About Developing Individualized Sequences of Health Interventions

Introduction to Adaptive Interventions and SMART Designs
8:05-8:35PM, Daniel Almirall and Susan Murphy, UMich

Q&A: 8:35-8:40PM

Adaptive Approach to Naltrexone Treatment for Alcoholism
8:40-9:10PM, David Oslin and Kevin Lynch, UPenn

Q&A: 9:10-9:15PM

Testing Variants of Treatments for Substance Use Disorders During Pregnancy
9:15-9:45PM, Hendree Jones, RTI

Q&A and Discussion: 9:45-10:00PM
Introduction to Adaptive Interventions and SMART Study Design Principles

Daniel Almirall\textsuperscript{1,2} Scott N Compton\textsuperscript{3} Susan A Murphy\textsuperscript{1,2,4}

\textsuperscript{1}Institute for Social Research, University of Michigan
\textsuperscript{2}The Methodology Center, Penn State University
\textsuperscript{3}Psychiatry and Behavioral Sciences, Duke University Medical Center
\textsuperscript{4}Department of Statistics, University of Michigan

Getting SMART About Developing Individualized Sequences of Health Interventions, CPDD, Hollywood, Florida
June 22, 2011
Outline

Adaptive Interventions
  What? Why?

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)

- **Responder**
  - Maintain: CBT
- **Non-Responders**
  - Add Treatment: CBT + MED

▶ Goal is to minimize the child’s symptom profile/trajectory.
What makes up an Adaptive Intervention?

1. Critical decisions: treatment options and more
2. Tailoring variables: to decide how to adapt treatment
3. Decision rules: inputs tailoring variable, outputs one or more recommended treatments

First-line Txt —— Tailoring Variable ———— Second-line Txt

- CBT
  - Responder
  - Non-Responders
  - 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

All require a sequences of treatment decisions.
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 interventions.
Motivation for an Example SMART
Child-Adolescent Anxiety Multi-modal Study (CAMS)

▶ CAMS was an acute-phase, efficacy, randomized clinical trial for pediatric anxiety disorders
▶ CBT+MED > MED ≈ CBT > Placebo
▶ However, families and clinicians remain concerned about the use of MED in this population
▶ An important next question for clinical practice is “Can we delay the use of MED?”
▶ Some children may do fine with CBT only and not need MED at all.
Concrete Example of a SMART: Pediatric Anxiety

- **CBT + MED**
  - Responders -> **R**
  - Non-Responders

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

**Non-Responders**

**R**

**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**
One Adaptive Intervention Within the SMART

CBT + MED

Non-Responders

Responders

Add Treatment: CBT + MED + FT
- Maintain: CBT + MED

Step Down: CBT Only
- Maintain: CBT
- Add Treatment: CBT + MED

Switch Treatment: MED

Non-Responders

R

O1 — First-line Txt — O2 + Primary Tailoring Variable — Second-line Txt — Y

R

CBT

R

Responders

R
Another Adaptive Intervention Within the SMART

CBT + MED

Non-Responders

CBT

Responders

CBT + MED

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

Responder

Non-Responders

R

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

AI 1
- CBT + MED
  - Non-Responders
  - Responders
  - Add Treatment: CBT + MED + FT
  - Step Down: CBT Boost

AI 2
- CBT + MED
  - Non-Responders
  - Responders
  - Maintain: CBT + MED
  - Add Treatment: CBT + MED + FT

AI 3
- CBT
  - Responders
  - Non-Responders
  - Maintain: CBT Boost
  - Add Treatment: CBT + MED

AI 4
- CBT
  - Responders
  - Non-Responders
  - Maintain: CBT Boost
  - Switch Treatment: MED
SMART Design Principles

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

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

▶ Use low dimensional summary to restrict subsequent treatments
  ▶ Use binary responder status
  ▶ Should be easy to use in actual clinical practice

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

▶ 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).

CBT + MED

Non-Responders

Responders

Add Treatment: CBT + MED + FT

Maintain: CBT + MED

Step Down: CBT Only

Add Treatment: CBT + MED

Switch Treatment: MED

CBT

Non-Responders

Responders

R

R

O1 ——— First-line Txt ————— O2 + Primary Tailoring Variable ——— Second-line Txt ——— Y

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Power

ES  | N |
---|---|
0.8 | 52 |
0.5 | 128|
0.2 | 788|

$\alpha = 0.05$

$\beta = 0.20$
Primary Aim Example 2
What is the main effect of first-line treatment? Longitudinal outcome (e.g., LMM).

Power

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$\rho = 0.60$
$\alpha = 0.05$
$\beta = 0.20$
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.

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

First-line Txt: CBT

→ Non-Responders

Second-line Txt: Y

R

Add Treatment: CBT + MED

Switch Treatment: MED

Almirall, Compton, Murphy

Experimental Designs for Developing Adaptive Interventions
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...

CBT + MED

Non-Responders

Responders

Add Treatment: CBT + MED + FT

Maintain: CBT + MED

Step Down: CBT Only

Maintain: CBT

Add Treatment: CBT + MED

Switch Treatment: MED
Discussion

- Adaptive Interventions are guides for clinical practice
- SMARTs do not necessarily require larger sample sizes
- SMARTs are used to build better Adaptive Interventions
  - Next trial will compare the SMART-optimized Adaptive Intervention versus usual care or other state-of-the-art treatment
Adaptive Treatment for Children with ADHD
PI: Pelham, Florida International University

**Medication**
- Responders → Continue Medication
- Non-Responders → Increase Medication Dose → Add Behavioral Intervention

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

Late Trigger for NR: 5+ HDD

8 Week Response

Non-Response

8 Week Response

Non-Response

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone
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 interventions 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