Experimental Designs for Developing Adaptive Treatment Strategies

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

Society of Behavioral Medicine, Washington, DC
April 26, 2011
Outline

Adaptive Treatment Strategies
  What? Why?
  ATS 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 Treatment Strategy

An adaptive treatment strategy (ATS) 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. ATSs operationalize sequential decision making with the aim of improving clinical practice.
Concrete Example of an Adaptive Treatment Strategy
Pediatric Anxiety Example (SAD, GAD, SoP)

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

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

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

- Responder
- Non-Responders

Almirall, Compton, Murphy
Designs for Developing Adaptive Treatment Strategies
Why Adaptive Treatment Strategies?
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
Why Adaptive Treatment Strategies?
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
Why Adaptive Treatment Strategies?
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

⇒ More personalized care, over time
⇒ Improving clinical practice
Developing an ATS Requires Careful Consideration

- For who are we developing the adaptive strategy? Population, or Context, question.

- What is the goal of the adaptive treatment strategy? 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
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 treatment strategies.
Concrete Example of a SMART: Pediatric Anxiety

- **CBT + MED**
  - **Non-Responders**
    - **R**
      - **Responders**
        - **R**
          - **CBT**
            - **Non-Responders**
          - **R**
    - **R**
      - **Maintain:**
        - **CBT**
          - **Add Treatment:**
            - **CBT + MED**
          - **Switch Treatment:**
            - **MED**
      - **Step Down:**
        - **CBT Only**
          - **Maintain:**
            - **CBT**
        - **R**
          - **Add Treatment:**
            - **CBT + MED**
          - **R**
            - **O2 + Primary Tailoring Variable**

- **First-line Txt**
- **Second-line Txt**
An ATS for Child Anxiety Within the SMART Add Treatment:
- CBT + MED + FT for Non-Responders
- CBT + MED Maintain:
  - CBT + MED
- Step Down:
  - CBT Only
- Add Treatment:
  - CBT + MED for Responders
- Switch Treatment:
  - MED

Tailoring Variable:
- First-line Txt
- Second-line Txt

Y

O1 ——————— First-line Txt ——————— O2 + Primary Tailoring Variable ——————— Second-line Txt ——— Y
Another ATS for Child Anxiety 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
SMART Design Principles

- KISS Principle: Keep It Simple, Straightforward
- Power for Simple Important Primary Hypotheses
- Take Appropriate Steps to Develop an Optimal ATS
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
  - Ex: Use $S = \text{binary responder status}$

- Collect rich set of outcomes for tailoring
  - Information useful for more complex ATSs
  - Think time-varying effect moderators
SMART Design: Primary Aims

Choose a **simple primary aim/question** that aids development of an adaptive treatment strategy.

Power the SMART to test this hypothesis.
Primary Aim Example 1

What is the main effect of first-line treatment?

<table>
<thead>
<tr>
<th>ES</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>52</td>
</tr>
<tr>
<td>0.5</td>
<td>128</td>
</tr>
<tr>
<td>0.2</td>
<td>788</td>
</tr>
</tbody>
</table>

\[
\alpha = 0.05 \quad \beta = 0.20
\]

Add Treatment: CBT + MED + FT  Non-Responders
CBT + MED Maintain: CBT + MED
Step Down: CBT Only
Responders
CBT

R

 Maintain: CBT
Add Treatment: CBT + MED
Switch Treatmnt: 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?

- **CBT + MED**
  - **Non-Responders** → **Add Treatment**: CBT + MED + FT
  - **Responders** → **Maintain**: CBT + MED
  - **Step Down**: CBT Only

- **CBT**
  - **Responders** → **Maintain**: CBT
  - **Non-Responders** → **Add Treatment**: CBT + MED
  - **Switch Treatment**: MED

**Tailoring Variable**

- First-line Txt
- Second-line Txt

**ES**

<table>
<thead>
<tr>
<th>ES</th>
<th>N</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

**Statistical Values**

- \( \rho = 0.60 \)
- \( \alpha = 0.05 \)
- \( \beta = 0.20 \)
Primary Aim Example 2
Which is the best of two fully-operationalized adaptive treatment strategies?

- **Add Treatment:**
  - CBT + MED + FT
- **Non-Responders**
- **Maintain:**
  - CBT + MED
- **Step Down:**
  - CBT Only
- **Switch Treatment:**
  - MED

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

- **Responder**

- **Non-Responders**

O1 ——— First-line Txt ——— O2 + Primary Tailoring Variable ——— Second-line Txt ——— Y
Choose secondary aims/questions that further develop the ATS 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
Secondary Aim Example 2
Develop a more deeply tailored adaptive treatment strategy.

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

Add Treatment: CBT + MED

Switch Treatment: MED

R
Examples SMART Designs

Examples of SMART designs which have been funded

- Pelham Study (primary analysis) Treatment of ADHD
- Oslin Study (primary analysis) Treatment of Alcohol Dependence
- Jones Study (in field) Treatment for Pregnant Women who are Drug Dependent
- Kasari Study (in field) Treatment of Children with Autism
- McKay Studies (2 in field) Treatment of Alcohol and Cocaine Dependence
Messages, Misconceptions, Misunderstandings

- Distinction between the ATS vs the SMART
  - Adaptive Trial? or Adaptive Treatment?

- SMARTs do not necessarily require larger sample sizes

- Distinction between adaptive vs non-adaptive treatments

- “Adaptive Design” has other meanings in trials literature
  - In SMART, same patients participate in multiple stages

- SMARTs can be seen as developmental trials
TOMORROW, WEDNESDAY 4/27

- 3-Hour Workshop on Adaptive Treatment Strategies and SMART designs
  - Instructors: Susan A. Murphy and Daniel Almirall
  - 3:10-6:00PM following Linda Collins’ workshop on MOST
  - Georgetown East, Concourse Level

Email me with questions about this presentation:

- dalmiral@umich.edu

These slides are 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
Non-Responders

Behavioral Intervention

Responders
Non-Responders

R

Continue Medication
Increase Medication Dose
Add Behavioral Intervention
Continue Behavioral Intervention
Increase Behavioral Intervention
Add Medication
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

T. Oslin, University of Pennsylvania
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 ATSs
  - 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 ATS

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 treatment strategy based on a myopic, local, study-to-study point of view may not be optimal.
Why Not Use Multiple Trials to Construct an ATS

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 ATS

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

**Negative Synergy Between 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.
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 ATS

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 treatment 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., childhood onset anxiety disorder)
- Outcome should incorporate time to initial response as a component
- Quick initial relief of symptoms should be valued