Experimental Designs for Developing Adaptive Treatment Strategies
With Application to the Management of Child Anxiety

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Outline

Adaptive Treatment Strategies
   What? Why?
   ATS Development Considerations

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

The Discontinuation Trial Alternative

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)

- child's history
- decision point
- tailoring variable
- decision point

- child w/anxiety responds to 12wks med+cbt
- step down: med only
- relapses
- responds
- augment: meds + cbt
- step down: no meds

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

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Designs for Developing Adaptive Treatment Strategies
Concrete Example of an Adaptive Treatment Strategy

Pediatric Anxiety Example (SAD, GAD, SoP)

A set of decision guidelines from clinician’s viewpoint

- Child with anxiety, responds to 12 wks med + cbt
- Step down: med only
- Responds
- Relapses
- Step down: no meds
- Augment: meds + cbt
Concrete Example of an Adaptive Treatment Strategy

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A treatment sequence from the child’s point of view
Concrete Example of an Adaptive Treatment Strategy

Pediatric Anxiety Example (SAD, GAD, SoP)

- child’s history
- decision point
- tailoring variable
- decision point

- child w/anxiety, responds to 12wks med+cbt
  - step down: med only
  - responds
  - step down: no meds
  - relapses
  - augment: meds + cbt

Another treatment sequence
Why Adaptive Treatment Strategies?
Necessary because...

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

- High child 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 child’s chronic/changing course
- Deliver appropriate treatment when needed most
- React to non-adherence or side-effect profiles
- Reduce treatment burden on the child
- Deliver early treatments with positive downstream effects
- Have ability to sift through available treatment options
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- ⇒ 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 are SMARTs?

What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- Multi-stage trials; same children participate throughout
- Each stage corresponds to a critical decision point
- At each stage, children are randomized to a set of treatment options
- Treatment options at randomization may be restricted depending on intermediate outcome/treatment history
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What is a Sequential Multiple Assignment Randomized Trial (SMART)?

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The goal of a SMART is to inform the development of adaptive treatment strategies.

⇒ Build the evidence base for adaptive treatment strategies.
Concrete Example of a SMART: Pediatric Anxiety

- Begin
- Decision point 1
- Tailoring variable
- Decision point 2
- 0-36 wks

**Children with anxiety, respond to 12 wks med + cbt**

- Step down: 12 wks med
- Step down: thru wk12
- Relapses by wk12
- Responds thru wk12

- Children who respond
- Continue: 12 wks med
- Step down: off txt

- Relapses by wk12
- Responds by wk12
- Augment: med + cbt
- Maintain: off txt

- Step up: med only
- Step up: cbt only

- Continuation phase

**R = Randomization**
An ATS for Child Anxiety Within the SMART

An Adaptive Strategy

- **begin**
- **decision pt 1**
- **tailoring var**
- **decision pt 2**
- **0-36 wks**

**continuation phase**

- **step down: 12wks med**
  - **children w/anxty, respond to 12wks med+cbt**
  - **responds thru wk12**
  - **relapses by wk12**
  - **step down: off txt**
  - **responds thru wk12**

- **continue: 12wks med**
- **step down: off txt**
- **augment: med + cbt**
- **step up: med only**
- **step up: cbt only**
- **maintain: off txt**

HEALTH OUTCOMES

0-36 wks

R

12wks med

decision pt 1 tailoring var decision pt 2

begin

12wks med

children w/anxty, respond to 12wks med+cbt

responds thru wk12

relapses by wk12

step down: off txt

An Adaptive Strategy
Another ATS for Child Anxiety Within the SMART

An Adaptive Strategy
decision pt 1 tailoring var decision pt 2
0-36 wks

begin
continuation phase
12wks med

children w/anxty, respond to 12wks med+cbt

step down: 12wks med

responds thru wk12

continue: 12wks med
step down: off txt

relapses by wk12

augment: med + cbt

step up: med only

maintenance

by wk12

relapses by wk12

step up: cbt only

maintain: off txt

off txt

responds thru wk12

step down: off txt

step down: thru wk12

R

R
What are Discontinuation Trials/Studies?
Sometimes called Maintenance Therapy Trials

In a discontinuation trial, participants that respond to an initial treatment during an acute phase are randomized to two or more discontinuation (or step down, maintenance, aftercare) strategies in the continuation phase.
Discontinuation Trials: Child Anxiety Disorder Example

begin
continuation phase

continue

step down:
24 weeks med

step down:
12 weeks med

children w/anxiety, respond to 12 wks med + cbt

R

step down:
off txt

begin
continuation phase

step down:
24 weeks med

step down:
0-36 wks

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H
R

respond
med + cbt
to 12 wks
children w/anxiety,
continuation
phase
begin
12 weeks med
step down:
Discontinuation Trials: Child Anxiety Disorder Example

Discontinuation Trials are motivated by scientific questions concerning adaptive treatment strategies.

Parent asks, “So how long does Bobby have to stay on medication?”

children w/anxty, respond to 12wks med+cbt

step down: 12weeks med

step down: 24weeks med

step down: off txt

children w/anxty, respond to 12wks med+cbt

Discontinuation Trials: Child Anxiety Disorder Example

begin
continuation phase

0-36 wks

HEALTH OUTCOMES

respond med+cbt

to 12wks med+cbt

step down: off txt

Discontinuation Trials are motivated by scientific questions concerning adaptive treatment strategies.

Parent asks, “So how long does Bobby have to stay on medication?”
Discontinuation Trials: Child Anxiety Disorder Example

Discontinuation Trials are typically analyzed using Survival Analysis Methods.

- **Step down:** 24 weeks med
- **Step down:** 12 weeks med
- **Step down:** Off txt

Children w/anxiety respond to 12 weeks med + cbt

Continuation phase

0-36 wks

Health outcomes
The Discontinuation Trial is Equivalent to this Trial

- Continue: 12wks med
- Step down: off txt
- Relapses by wk12
- Step down: off txt
- Responds thru wk12
- Children w/anxiety, respond to 12wks med + cbt
- Step down: off txt
- Maintain: off txt
- Decision pt 2
- 0-36 wks

R = Randomization

HEALTHOUTCOMES

Decision pt 1
Tailoring var

Continuation phase

Begin

12wks med

Relapses by wk12

Responds thru wk12

Children w/anxiety, respond to 12wks med + cbt
The Discontinuation Trial is Subsumed by the SMART

- **begin**
- **decision pt 1**
- **tailoring var**
- **decision pt 2**
- **0-36 wks**

**continuation phase**

**R=Randomization**

**children w/anxiety, respond to 12wks med+cbt**

**step down: 12wks med**

- responds thru wk12

**step down: off txt**

- children w/anxiety, respond to 12wks med+cbt

**relapses by wk12**

- augments med + cbt
- step up: med only
- step up: cbt only

**continue: 12wks med**

- maintenance: off txt
Why use SMARTs in place of Discontinuation Trials?

- A SMART can be designed to address the typical medication discontinuation questions, plus more
- SMARTs can address more meaningful questions that are more in-line with actual clinical practice
- Participants can be used more efficiently in SMARTs
- Sequential randomization can be used to ensure better comparability of treatment options at intermediate decision points
- The SMART does not prohibit a survival analysis for the questions related to discontinuation
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 for the SMART only by ethical, feasibility, or strong scientific considerations

- Use low dimensional summary instead of all intermediate outcomes to restrict subsequent treatments
  - Ex: Use $S = \text{binary responder status}$

- Collect rich set of intermediate outcomes that might be useful in deciding later for whom treatment works best
  - Information useful for more complex ATSs
  - Think time-varying effect moderators
SMART Design: Primary Hypothesis

Choose a primary hypothesis that aids development of an adaptive treatment strategy. Power the SMART to test this hypothesis.

Child Anxiety Example: Among children who respond to eight weeks of combination therapy, who are then discontinued from cbt, which step-down strategy is better in terms of shorter time to relapse: (1) discontinue meds immediately, (2) discontinue meds at week 12, or (3) discontinue meds at week 24.
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**The original Discontinuation Trial primary hypothesis!**
SMART Design: Primary Hypothesis

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**The original Discontinuation Trial primary hypothesis!** Others are also possible, such as comparing different ATSs.
SMART Design: Secondary Hypotheses

Choose secondary hypotheses that further develop the ATS and take advantage of sequential randomization to eliminate confounding.

**Child Anxiety Example:**

- Meds only (0-12wks)
- Step down: off txt
- Continue: meds only

Adherence, side-effects (0-12wks)

... responder

through week 12

12-24 weeks

0-36 wks

O U T C O M E S
SMART Design: Secondary Hypotheses

Choose *secondary hypotheses* that further develop the ATS and take advantage of sequential randomization to eliminate confounding.

**Child Anxiety Example:**

<table>
<thead>
<tr>
<th>0-12 weeks</th>
<th>12-24 weeks</th>
<th>0-36 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>relapses</td>
<td>step up:</td>
<td>OUTCOMES</td>
</tr>
<tr>
<td>off txt</td>
<td>med only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>step up:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cbt only</td>
<td></td>
</tr>
<tr>
<td>txt preface, decline rte upto relps</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

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Designs for Developing Adaptive Treatment Strategies
Messages, Misconceptions, Misunderstandings

- Distinction between the ATS vs the SMART
  - Adaptive Trial? or Adaptive Treatment?
- “Adaptive Design” has other meanings in trials literature
  - In SMART, same patients participate in multiple stages
- SMARTs generalize Discontinuation Trials/Studies
- SMARTs do not require larger sample sizes
- Distinction btwn adaptive vs non-adaptive treatments
- SMARTs can be seen as developmental trials
  - 1. Run a SMART
  - 2. Run a Confirmatory Trial: Optimized ATS vs Control
  - This is not a criticism of SMARTs
Thank You!

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Special supplement on ATSs & SMARTs: Customizing Treatment to the Patient: Adaptive Treatment Strategies. *Drug and Alcohol Dependence*. May 2007; 88 (Supplement 2), ppS1-S72. Please see me after the talk for a copy.

For a wealth of information, see:
www.stat.lsa.umich.edu/~samurphy
Extra Slides
SMART Designs in the Field/Literature
Examples of SMARTs that are Underway or Under Review

- Pelham Study (on going) Treatment of ADHD
- Oslin Xtend Study (on going) Treatment of Alcohol Dependence
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 ATGs
  - 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 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 ATS

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 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 within-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