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?

Other Study Design Alternatives

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.

ATSs are also known as: treatment algorithms, stepped care interventions, dynamic treatment regimes, discontinuation or augmentation strategies, structured treatment interruptions, tailored interventions, ...
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: relapses

responds

augment: meds + cbt

step down: no meds

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

A set of decision guidelines from clinician’s viewpoint

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Designs for Developing Adaptive Treatment Strategies
Concrete Example of an Adaptive Treatment Strategy
Pediatric Anxiety Example (SAD, GAD, SoP)

A treatment sequence from the child’s point of view

- child w/anxty, responds to 12wks med+cbt
- step down: med only
- relapses
- respond
- augmented: meds + cbt
- step down: no meds

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Concrete Example of an Adaptive Treatment Strategy

Pediatric Anxiety Example (SAD, GAD, SoP)

- child’s history: child w/anxiety, responds to 12wks med+cbt
- decision point: step down: med only
- tailoring variable: responds
- decision point: augment: meds + cbt
- step down: no meds

▶ Another treatment sequence

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Designs for Developing Adaptive Treatment Strategies
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 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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- 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.
- ⇒ Build the evidence base for adaptive treatment strategies.
Concrete Example of a SMART: Pediatric Anxiety

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

**continuation phase**

**R** = Randomization

**step down:**
- 12wks med
  - responds thru wk12
  - relapses by wk12
  - responds thru wk12

**step down:**
- off txt

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

**step down:**
- 12wks med
  - responds thru wk12
  - relapses by wk12

**step down:**
- off txt

**continue:**
- 12wks med
  - step down:
    - off txt

**augment:**
- med + cbt
  - step up:
    - med only
    - cbt only
  - maintain:
    - off txt
An ATS for Child Anxiety Within the SMART

An Adaptive Strategy
Another ATS for Child Anxiety Within the SMART

begin

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

step down: 12wks med

R

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

step down: off txt

An Adaptive Strategy

tailoring var

responds thru wk12

relapses by wk12

R

R

relapses by wk12

continue: 12wks med

step down: off txt

step up: med only

step up: cbt only

maintain: off txt

decision pt 2

0-36 wks

continued phase

decision pt 1

R

R

R

R

HEALTH OUTCOMES
Other Study Design 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

▶ RCTs of Pre-specified Adaptive Treatment Strategies

▶ 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

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Designs for Developing Adaptive Treatment Strategies
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

- KISS Principle: Keep It Simple, Straightforward
- Power for Simple Important Primary Hypotheses
- Take Appropriate Steps to Develop an Optimal ATS
- Choose a Longitudinal Outcome
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
  ► Think tailoring variables
SMART Design: Primary Hypothesis

Ex 1: Primary Hypothesis: * versus **

R=Randomization
SMART Design: Primary Hypothesis

Ex 1: Primary Hypothesis: * versus **

R=Randomization

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<td>0.5</td>
<td>128</td>
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<td>0.8</td>
<td>52</td>
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α = 0.05
β = 0.20

0-8 weeks 8-12 weeks by week 12 12-16 weeks 0-24 wks

HEALTH OUTCOMES

responds
med+cbt

medi only

* responder

R

taper off txt

** non responder

augment: med + cbt

augment: med only

non responder

switch cbt only

continue: meds only

maintain off txt

ES 0.2 788 0.5 128 0.8 52

α = 0.05
β = 0.20
SMART Design: Secondary Hypotheses

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

Child Anxiety Example:

- **Responder**
- **Med only**
- Adherence, side-effects (0-12 wks)
- Continue: meds only
- Step down: off txt

... thru week 12 12-24 weeks 0-36 wks

OUTCOMES

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SMART Design: Secondary Hypotheses

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

**Child Anxiety Example:**

0-12weeks 12-24weeks 0-36 wks

- **relapses off txt**
- **txt preface, decline rte upto relps**
- **step up: cbt only**
- **step up: med only**

\[ R \]

\[ \text{OUTCOMES} \]
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
- Taking advantage of with-in person variability leads to increased statistical precision (this means more power, smaller sample size)
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 between 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
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See Special Supplement in *Drug and Alcohol Dependence*:

- **Customizing Treatment to the Patient: Adaptive Treatment Strategies.** *Drug and Alcohol Dependence.*
- May 2007; 88 (Supplement 2), ppS1-S72.

For a wealth of information, see:
www.stat.lsa.umich.edu/~samurphy/research.html
Extra Slides
SMART Designs in the Field/Literature

- Pelham Study (on going) Treatment of ADHD
- Oslin Xtend Study (on going) Treatment of Alcohol Dependence
- Jones Study (on going) Treatment for Drug Abusing Pregnant Women

These seminal studies have many of the same features that SMARTs have:

- CATIE: Clinical Antipsychotic Trials in Intervention Effectiveness
- STAR*D: Sequenced Treatment Alternatives to Relieve Depression
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

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

step down: 12weeks med

step down: 24weeks med

step down: off txt

0-36 wks

HEALTH OUTCOMES
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/anxiety, respond to 12wks med+cbt

begin continuation phase

step down: 24 weeks med

step down: 12 weeks med

step down: off txt

0-36 wks

HEALTH OUTCOMES
Discontinuation Trials: Child Anxiety Disorder Example

Discontinuation Trials are typically analyzed using Survival Analysis Methods.

**begin**

**continuation phase**

- **step down:** 24 weeks med
- **step down:** 12 weeks med
- **step down:** off txt

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

**0-36 wks**

**OUTCOMES**

**HEALTH**
The Discontinuation Trial is Equivalent to this Trial

- **begin**: continue
- **decision pt 1**: tailoring var
- **decision pt 2**: 0-36 wks
- **continuation phase**: children w/anxiety, respond to 12wks med+cbt

**R** = Randomization

- step down: 12wks med
  - responds thru wk12
    - continue: 12wks med
    - step down: off txt
      - ?
      - maintain: off txt

- step down: off txt
  - relapses by wk12
    - ?

- relapses by wk12
  - responds thru wk12

**HEALTH OUTCOMES**
The Discontinuation Trial is Subsumed by the SMART

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

**continuation phase**

- **step down: 12wks med**
  - responds thru wk12
  - R

- **relapses by wk12**
  - augment: med + cbt
  - step up: med only
  - step up: cbt only

- **children w/anxty, respond to 12wks med+cbt**
  - R
  - step down: off txt

- **responds thru wk12**
  - maintain: off txt

**H E A L T H O U T C O M E S**
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