Getting SMART About Developing Individualized Sequences of Health Interventions

University of Minnesota, June 8

Susan A. Murphy & Daniel Almirall
Outline

- **MODULE 1**: Adaptive Treatment Strategies  
  (Murphy: 9:15-9:55AM)
- **MODULE 2**: SMART Experimental Design  
  (Murphy: 10:20-11:10AM)
- **MODULE 3**: Preparing for a SMART  
  (Almirall: 11:40-12:10PM)
- **MODULE 4**: Interesting Primary Data Analyses  
  (Almirall: 2:00-2:50PM)
- **MODULE 5**: Interesting Secondary Data Analyses  
  (Almirall: 3:20-4:10PM)

With discussion, exercises, lunch, and breaks in between.
Adaptive Treatment Strategies

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Outline

• What are Adaptive Treatment Strategies?
• Why use Adaptive Treatment Strategies?
• Adaptive Treatment Strategy Design Goals
• What does an Adaptive Treatment Strategy include?
• Summary & Discussion
Adaptive Treatment Strategies

- Are individually tailored time-varying treatments composed of
  - a sequence of critical treatment decisions
  - tailoring variables
  - decision rules, one per critical decision; decision rules input tailoring variables and output individualized treatment recommendation(s).

- Operationalize clinical practice.
Adaptive Aftercare for Alcohol Dependent Individuals

• Overall goal: prevent relapse to alcohol abuse

• Critical treatment decisions: which treatment to provide first?; which treatment to provide second?

• Tailoring variable: heavy drinking days
Decision Rules

First alcohol dependent individuals are provided Naltrexone along with Medical Management.

IF an individual experiences 3 or more heavy drinking days prior to 8 weeks
    THEN the individual’s Naltrexone treatment is augmented with Combine Behavioral Intervention.

ELSE IF the individual successfully completes 8 weeks with fewer than 3 heavy drinking days
    THEN the individual is provided a prescription to Naltrexone along with Telephone Disease Management.
Adaptive Treatment Strategies

- From the individual/patient/client’s point of view: a sequence of (individualized) treatments

- From the clinical scientist’s point of view: a sequence of decision rules that recommend one or more treatments at each critical decision.
More examples of critical treatment decisions and tailoring variables

- **Critical treatment decisions:** how long to try the first treatment?; how should a treatment be delivered?; how intensive should a treatment be? When to stop/start treatment?

- **Tailoring variables:** severity of illness, presence of comorbid mental or physical conditions, family support, adherence to present treatment, side effects resulting from present treatment, symptoms while in treatment.
Another Example of an Adaptive Treatment Strategy

• Adaptive Drug Court Program for drug abusing offenders.

• Goal is to minimize recidivism and drug use.

• Marlowe et al. (2008)
Adaptive Drug Court Program

- As-needed court hearings + standard counseling (low risk)
  - Bi-weekly court hearings + standard counseling (high risk)
    - As-needed court hearings + ICM (non-responsive)
      - As-needed court hearings + ICM (non-compliant)
  - As-needed court hearings + ICM (non-responsive)
    - As-needed court hearings + ICM (non-compliant)
    - Court-determined disposition (non-compliant)
Other Examples of Adaptive Treatment Strategies

• Brooner et al. (2002, 2007) Treatment of Opioid Addiction

• McKay (2009) Treatment of Substance Use Disorders

• Marlowe et al. (2008) Drug Court

• Rush et al. (2003) Treatment of Depression
Outline

• What are Adaptive Treatment Strategies?
• Why use Adaptive Treatment Strategies?
• Adaptive Treatment Strategy Design Goals
• What does an Adaptive Treatment Strategy include?
• Summary & Discussion
Why Adaptive Treatment Strategies?

1) High heterogeneity in need for or response to any one treatment

What works for one person may not work for another, thus often need a sequence of treatments just to obtain an acute response
Why Adaptive Treatment Strategies?

2) Chronic or Waxing and Waning Course

Improvement often marred by relapse

Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

• Treatment incurs side effects and substantial burden, particularly over longer time periods.
• Problems with adherence:
  • Variations of treatment or different delivery mechanisms may increase adherence
  • Excessive treatment may lead to non-adherence
• Treatment is costly (Would like to devote additional resources to patients with more severe problems)

More is not always better!
Outline

• What are Adaptive Treatment Strategies?
• Why use Adaptive Treatment Strategies?
• Adaptive Treatment Strategy Design Goals
• What does an Adaptive Treatment Strategy include?
• Summary & Discussion
Treatment Design Goals

• Maximize the strength of the adaptive treatment strategy
  • by well chosen tailoring variables, well measured tailoring variables, & well conceived decision rules
Treatment Design Goals

• Maximize replicability in future experimental and real-world implementation conditions
  • by fidelity of implementation & by clearly defining the treatment strategy
Design Considerations

• Choice of the Tailoring Variable
• Measurement of the Tailoring Variable
• Decision Rules linking Tailoring Variables to Treatment Decisions
• Implementation of the Decision Rules
Tailoring Variables

• Significant differences in effect sizes in a comparison of fixed treatments as a function of characteristics.

• That is, some values of the tailoring variable should indicate a particular treatment decision is best while other values of the tailoring variable should indicate that a different treatment decision is best.
Adaptive Aftercare for Alcohol Dependent Individuals

• Individuals who return to heavy drinking while on Naltrexone need additional help to maintain a non-drinking lifestyle.
• Tailoring variable is heavy drinking
• Providing CBI to individuals who are maintaining a non-drinking lifestyle is costly.
Technical Interlude!

$s=$tailoring variable
$t=$treatment type (0 or 1)
$Y=$primary outcome (high is preferred)

$Y=\beta_0 + \beta_1 s + \beta_2 t + \beta_3 st + error$

$= \beta_0 + \beta_1 s + (\beta_2 + \beta_3 s)t + error$

If $(\beta_2 + \beta_3 s)$ is zero or negative for some $s$ and positive for others then $s$ is a tailoring variable.
**S** is a **moderator variable** because the magnitude of the effect of **Tx=1** versus **Tx=0** differs by levels of **S**.

**S** is **not a tailoring variable**: Offer **Tx=0** to all subjects to maximize **Y**.

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**S** is a **weak tailoring variable** because the direction of the effect of **Tx=1** versus **Tx=0** differs by levels of **S** but magnitude is small.

**S** is **somewhat prescriptive**: Offer **Tx=0** to **S=0** subjects; offer **Tx=1** to **S=1** subjects, but the difference in effects is not substantial.

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**S** is a **strong tailoring variable** because the direction of the effect of **Tx=1** versus **Tx=0** differs by levels of **S**.

**S** is **very prescriptive**: Offer **Tx=0** to **S=0** subjects; offer **Tx=1** to **S=1** subjects. Large magnitudes of clinical significance.
Measurement of Tailoring Variables

• Reliability -- high signal to noise ratio

• Validity -- unbiased
Derivation of Decision Rules

• Articulate a theoretical model for how treatment effect on key outcomes should differ across values of the moderator.

• Use prior clinical experience.

• Use prior experimental and observational studies.

• Discuss with research team and clinical staff, “What dosage would be best for people with this value on the tailoring variable?”
Derivation of Decision Rules

• Good decision rules are objective, are operationalized.

• Strive for comprehensive rules (this is hard!) – cover situations that can occur in practice, including when the tailoring variable is missing or unavailable.
• Try to implement rules universally, applying them consistently across subjects, time, site & staff members.

• Document values of tailoring variable!
Implementation

• Exceptions to the rules should be made only after group discussions and with group agreement.

• If it is necessary to make an exception, document this so you can describe the implemented treatment.
• Research is needed to build a theoretical literature that can provide guidance:
  • in identifying tailoring variables,
  • in the development of reliable and valid indices of the tailoring variables that can be used in the course of repeated clinical assessments
Summary & Discussion

• Given a structural model of the causal chain relating the tailoring variables, decisions and outcome, statistical methods can help construct the decision rules

  • Influence diagrams and graphical models (a way to efficiently encode expert knowledge—R. Shachter, S. Lauritzen)
Questions?

More information


Discussion & Practice Exercise

Exercise: Write down 2-3 simple ATSSs to address a chronic disorder in your field!

Next up!: Experimental Study designs for use in finding good tailoring variables and rules.
Sequential, Multiple Assignment, Randomized Trials

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The Big Questions in Adaptive Treatment Strategy Development

• What is the best sequencing of treatments?

• What is the best timings of alterations in treatments?

• What information do we use to make these decisions? (how do we individualize the sequence of treatments?)

The purpose of the SMART study is to provide high quality data for addressing these questions.
Outline

• What are Sequential Multiple Assignment Trials (SMARTs)?
• Why SMART experimental designs?
• Trial Design Principles
• Examples of SMART Studies
• Summary & Discussion
What is a SMART Study?

What is a sequential multiple assignment randomized trial (SMART)?

These are multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

Goal is to inform the construction of adaptive treatment strategies.
Sequential Multiple Assignment Randomization

Initial Txt | Intermediate Outcome | Secondary Txt
---|---|---
Tx A

Nonresponder

Early Responder

R

R

R

Tx B

Nonresponder

Early Responder

R

R

R

Switch to Tx C

Augment with Tx D

Switch to Tx C

Augment with Tx D

Relapse Prevention

Low-level Monitoring

Relapse Prevention

Low-level Monitoring
One Adaptive Treatment Strategy

**Initial Txt**

1. **Tx A**
   - Early Responder
   - Nonresponder

**Intermediate Outcome**

- Early Responder
- Nonresponder

**Secondary Txt**

- Relapse Prevention
- Low-level Monitoring
- Switch to Tx C
- Augment with Tx D

**Relapse**

- Tx B
  - Early Responder
  - Nonresponder

- Augment with
Outline

• What are Sequential Multiple Assignment Trials (SMARTs)?
• Why SMART experimental designs?
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• Summary & Discussion
Challenges in constructing Adaptive Treatment Strategies

• Delayed, Prescriptive & Sample Selection Effects

  ---sequential multiple assignment randomized trials (SMART)

• Dynamic Treatment Regimes are Multi-component Treatments

  ---series of screening/refining randomized trials prior to confirmatory trial (MOST).
Alternate Approach I to Constructing an Adaptive Treatment Strategy

• Why not use data from multiple trials to construct the adaptive treatment strategy?

• Choose the best initial treatment on the basis of a randomized trial of initial treatments and choose the best secondary treatment on the basis of a randomized trial of secondary treatments.
Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Positive synergies: Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment. Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.
Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Negative synergies: Treatment A may produce a higher proportion of responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond. Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.
Prescriptive Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Treatment A may not produce as high a proportion of responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.
Sample Selection Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Subjects who will enroll in, who remain in or who are adherent in the trial of the initial treatments may be quite different from the subjects in SMART.
Summary:

• When evaluating and comparing initial treatments, *in a sequence of treatments*, we need to take into account, e.g. control, the effects of the secondary treatments thus SMART.

• Standard one-stage randomized trials may yield information about different populations from SMART trials.
Alternate Approach II to Constructing an Adaptive Treatment Strategy

Why not use theory, clinical experience and expert opinion to construct the adaptive treatment strategy and then compare this strategy against an appropriate alternative in a confirmatory randomized two group trial?
Why constructing a dynamic treatment regime and then comparing the regime against a standard alternative is not always the answer.

- Don’t know why your adaptive treatment strategy worked or did not work. Did not open black box.
- Adaptive treatment strategies are high dimensional multi-component treatments
- We need to address: when to start treatment?, when to alter treatment?, which treatment alteration?, what information to use to make each of the above decisions?
Meeting the Challenges

Delayed/Prescriptive/Sample Selection Effects: SMART

High Dimensionality: Screening/refining randomized trials prior to a confirmatory trial (MOST).

The SMART design is one of the screening/refining randomized trials in MOST.
Sequential Multiple Assignment Randomization

- **Initial Txt**
  - Early Responder
    - Nonresponder
      - Nonresponder
        - Nonresponder
          - Nonresponder

- **Intermediate Outcome**
  - Relapse Prevention
    - Low-level Monitoring
      - Switch to Tx C
        - Augment with Tx D
          - Augment with Tx D

- **Secondary Txt**
  - Early Relapse
    - Responder
      - Relapse Prevention
        - Low-level Monitoring
          - Switch to Tx C
            - Augment with Tx D
Examples of “SMART” designs:

• CATIE (2001) Treatment of Psychosis in Schizophrenia

• Pelham (primary analysis) Treatment of ADHD

• Oslin (primary analysis) Treatment of Alcohol Dependence

• Jones (in field) Treatment for Pregnant Women who are Drug Dependent

• Kasari (in field) Treatment of Children with Autism

• McKay (in field) Treatment of Alcohol and Cocaine Dependence
Outline

• What are Sequential Multiple Assignment Trials (SMARTs)?
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SMART Design Principles

- **KEEP IT SIMPLE**: At each stage (critical decision point), restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

- Collect intermediate outcomes that might be useful in ascertaining for whom each treatment works best; information that might enter into the adaptive treatment strategy.
SMART Design Principles

• Choose primary hypotheses that are both scientifically important and aids in developing the adaptive treatment strategy.
  • Power trial to address these hypotheses.

• Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.
  • Trial is not necessarily powered to address these hypotheses.
SMART Designing Principles: Primary Hypothesis

• EXAMPLE 1: *(sample size is highly constrained)*: Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

• EXAMPLE 2: *(sample size is less constrained)*: Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.
EXAMPLE 1

Initial Tx

Intermediate Outcome

Tx A

Early Responder

Nonresponder

Relapse Prevention

Low-level Monitoring

Switch to Tx C

Augment with Tx D

Secondary Tx

Tx B

Early Responder

Nonresponder

Relapse Prevention

Low-level Monitoring

Switch to Tx C

Augment with Tx D
EXAMPLE 2

Initial Tx: Tx A

Intermediate Outcome:
- Early Responder
- Nonresponder

Secondary Tx:
- Relapse Prevention
- Low-level Monitoring
- Switch to Tx C
- Augment with Tx D

Switch to Tx C
- Early Responder
- Nonresponder

Augment with Tx D
- Early Responder
- Nonresponder

Low-level Monitoring
- Early Responder
- Nonresponder

Nonresponder
SMART Designing Principles: Sample Size Formula

• EXAMPLE 1: (sample size is highly constrained): Hypothesize that given the secondary treatments provided, the initial treatment A results in lower symptoms than the initial treatment B. *Sample size formula is same as for a two group comparison.*

• EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D. *Sample size formula is same as a two group comparison of non-responders.*
## Sample Sizes

$N =$ trial size

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta \mu/\sigma = 0.3$</td>
<td>$N = 402$</td>
</tr>
<tr>
<td>$\Delta \mu/\sigma = 0.5$</td>
<td>$N = 146$</td>
</tr>
</tbody>
</table>

$\alpha = 0.05, \quad \text{power} = 1 - \beta = 0.85$
An analysis that is less useful in the development of adaptive treatment strategies:

Decide whether treatment A is better than treatment B by comparing intermediate outcomes (proportion of early responders).
SMART Designing Principles

• Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.

• EXAMPLE: Hypothesize that non-adhering non-responders will exhibit lower symptoms if their treatment is augmented with D as compared to an switch to treatment C (e.g. augment D includes motivational interviewing).
EXAMPLE 2

Initial Txt  Intermediate Outcome  Secondary Txt

Tx A  Nonresponder  Switch to Tx C

Tx B  Early Responder  Relapse Prevention

Tx B  Nonresponder  Augment with Tx D

Tx A  Early Responder  Relapse Prevention

Tx A  Low-level Monitoring

Tx B  Low-level Monitoring

Switch to Tx C

Augment with Tx D

Augment with Tx D
Outline

• What are Sequential Multiple Assignment Trials (SMARTs)?
• Why SMART experimental designs?
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Kasari Autism Study

A. JAE + EMT
Random assignment:

12 weeks
Assess-
Adequate response?

Yes
JAE + EMT
JAE+EMT+++

No
Random assignment:

B. JAE + AAC

12 weeks
Assess-
Adequate response?

Yes
B1. JAE + AAC
B2. JAE + AAC ++
Pelham ADHD Study

A. Begin low-intensity behavior modification

Random assignment:

B. Begin low dose medication

Random assignment:

A1. Continue, reassess monthly; randomize if deteriorate

A2. Add medication; bemod remains stable but medication dose may vary

A3. Increase intensity of bemod with adaptive modifications based on impairment

B1. Continue, reassess monthly; randomize if deteriorate

B2. Increase dose of medication with monthly changes as needed

B3. Add behavioral treatment; medication dose remains stable but intensity of bemod may increase with adaptive modifications based on impairment
Jones’ Study for Drug-Addicted Pregnant Women

Random assignment:

2 wks Response

rRBT

Random assignment:

Nonresponse

tRBT

eRBT

Random assignment:

2 wks Response

rRBT

Random assignment:

Nonresponse
	aRBT

rRBT

tRBT

rRBT
Osling ExTENd

Early Trigger for Nonresponse

Random assignment:

Late Trigger for Nonresponse

Random assignment:

8 wks Response

Random assignment:

TDM + Naltrexone

CBI

Naltrexone

CBI + Naltrexone

8 wks Response

Random assignment:

TDM + Naltrexone

CBI

CBI + Naltrexone

Nonresponse

Random assignment:

Nonresponse

Random assignment:
Summary & Discussion

• We have a sample size formula that specifies the sample size necessary to detect an adaptive treatment strategy that results in a mean outcome $\delta$ standard deviations better than the other strategies with 90% probability.

• We also have sample size formula that specify the sample size for time-to-event studies.

See
http://methodology.psu.edu/downloads
Questions?

More information


Practice Exercise

Exercise: Using your 2-3 simple ATSSs, (a) construct a draft SMART design and (b) identify your primary scientific aim!

Next up!: Preparing for a SMART: preliminary Studies and Pilots.
Preparing for a SMART Study

Getting SMART About Developing Individualized Sequences of Health Interventions

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Daniel Almirall & Susan A. Murphy
Outline

• We discuss scientific, logistical, and statistical issues specific to executing a SMART that should be considered when planning a SMART (e.g., in a SMART pilot study)
• Sample size calculation for SMART pilots
Primary Aim of Pilot Studies (in general)

• Is to examine feasibility of full-scale trial: e.g.,
  – Can investigator execute the trial design?
  – Will participants tolerate treatment?
  – Do co-investigators buy-in to study protocol?
  – To manualize treatment(s)
  – To devise trial protocol quality control measures

• Is **not** to obtain preliminary evidence about efficacy of a treatment or treatment strategy.
Review the ADHD SMART Design
PI: Dr. Pelham, FIU

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

Behavioral Intervention
- Responders
  - Continue Behavioral Intervention
  - Increase Behavioral Intervention
  - Add Medication
- Non-Responders
  - Responders
  - Non-Responders
Primary/Design Tailoring Variable

• Explicitly/clearly define early non/response

• We recommend binary measure
  – Theory, prior research, conventions, and/or preliminary data can be used to find a cut-off.

• Need estimate of the non/response rate
  – Using data from prior trials; or maybe in a pilot

• Should be associated with long-term response
  – Surrogate marker or mediation theories

• Should be easily assessed/measured in practice
Protocol for Missing Primary Tailoring Variable

• Suppose participant misses clinic visit when the primary tailoring variable is assessed
  – How do we assign second stage treatment if/when participant returns?

• This is a non-standard missing data issue

• Need a fixed, pre-specified protocol for determining responder status based on whether/why primary tailoring variable is missing. Guided by actual clinical practice.
Example Protocol for Missing Primary Tailoring Variable

• Need a fixed, pre-specified protocol for determining responder status based on whether/why primary tailoring variable is missing. Guided by actual clinical practice.

• Example 1: Classify all participants with missing response as non-responders.

• Example 2: Classify all participants with missing response as responders.
Manualizing Treatment Strategies

• Recall: SMART participants move through stages of treatment as part of embedded ATSs
• Treatment strategies are manualized
  – Not just the treatment options by themselves
  – Includes transitions between treatment options
• Treatment has an expanded definition
  – Example: stepping down is a treatment decision
• Recall: randomization is not part of treatment
Prepare to Collect Other Potential Tailoring Variables

- Additional variables used in secondary aims that could be useful in tailoring treatment
- Pilot new scales, instruments, or items that could be used as tailoring variables in practice
- Have protocols for discovering additional unanticipated tailoring variables:
  - Process measures (e.g., allegiance with therapist)
  - Use focus groups during and at end of pilot
  - Use exit interviews during and at end of pilot
Evaluation Assessment versus Treatment Assessment

• Makes sense to use (blinded) independent evaluators to collect outcomes measures used to evaluate effectiveness of embedded ATS
• But it is acceptable to use treating clinicians to measure the primary tailoring variable used to move to second-stage of treatment
• SMART Pilot study can be used to practice protocols to keep these distinct
Staff Acceptability to Changes in Treatment

• Challenges in a SMART:
  – Researchers maybe not accustomed to protocolized treatment *sequences*/*strategies*
  – SMART may limit use of clinical judgement

• Use a pilot SMART to identify concerns by staff and co-investigators about
  – Assessment of early non/response
  – Sequences of treatment provided

• Ex: clinician wants to classify early-nonrspder
Participant Adherence/concerns about Changes in Treatment

• Use the pilot SMART to identify concerns by participants using
  – Focus groups, exit interviews, or additional survey items

• May ask participants about
  – Experience transitioning between treatments
  – Was rationale for treatment changes adequate?
  – Was appropriate information you shared with clinician(s) in stage 1 understood by stage 2 clinician(s)?
Randomization Procedure

• A SMART pilot will allow investigators to practice randomization procedures

• Up-front versus real-time randomization
  – Up-front: After baseline, randomize participants to the embedded ATSs
  – Real-time: Randomize sequentially

• We recommend real-time because we can balance randomized second stage options based on responses to initial treatment.
Sample Size for a SMART Pilot

- Sample size calculation based on feasibility aims, not treatment effect detection/evaluation
- **Approach 1**: Primary feasibility aim is to ensure investigative team has opportunity to implement protocol from start to finish.
  - Assume: Need 2-3 children in each of the 6 cells
  - Assume: 10% drop out, 40% response rate
  - Need to recruit approximately 20 children for the SMART pilot study
ADHD SMART Design (PI: Pelham)

R
N=18

Medication
N=9

Responders
N=3

Non-Responders
N=6

Behavioral Intervention
N=9

Responders
N=3

Non-Responders
N=6

Continue Medication
N=3

Increase Medication Dose
N=3

Add Behavioral Intervention
N=3

Continue Behavioral Intervention
N=3

Increase Behavioral Intervention
N=3

Add Medication
N=3
Sample Size for a SMART Pilot

- **Approach 2**: To obtain estimate of overall non/response rate with a given margin of error
  - This is a more statistical justification
  - Usually requires larger sample than Approach 1
  - Use this approach if there is very poor information available about non/response rate

- $95\% \text{ MOE} = 2 \times \sqrt{\frac{p(1-p)}{N}}$

- **Example 1**: $p=0.35$, MOE=0.15 requires $N=41$
- **Example 2**: $p=0.50$, MOE=0.10 requires $N=100$
susan i don't love this. this approach always ends up requiring large N. i think it may be most useful it investigators have no idea what response rate is and they are worried it is too large or too small

dalminal, 6/6/2011
Citations

• Almirall D, Compton SN, Gunlicks-Stoessel M, Duan N, Murphy SA (under review). Designing a Pilot SMART for Developing an Adaptive Treatment Strategy.
  – Will be available as Technical Report soon!

• Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *Journal of Psychiatry Research.*

• Kraemer HC et al. (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. *Arch Gen Psychiatry.*
Practice Exercise

**Exercise:** Write down data sources available to you that you could use as preliminary data for a SMART. If you would like to do a SMART pilot, what is the primary feasibility aim?

Next up: Primary Aims Using Data Arising from a SMART
Primary Aims Using Data Arising from a SMART

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Daniel Almirall & Susan A. Murphy
Primary Aims Outline

• Review the *Adaptive Interventions for Children with ADHD Study* design
  – This is a SMART design

• Two typical primary research questions in a SMART
  – Q1: Main effect of first-line treatment?
  – Q2: Comparison of two embedded ATSs?

• Results from a worked example

• SAS code snippets for the worked example
Review the ADHD SMART Design

- **Medication**
  - Responders
  - Non-Responders

- **Behavioral Intervention**
  - Responders
  - Non-Responders

- **R**
  - Continue Medication
  - Increase Medication Dose
  - Add Behavioral Intervention

- **O1** → **A1** → **O2 / R Status** → **A2** → **Y**
There are 2 “first Line” treatment decisions

Responders
- Continue Medication
- Increase Medication Dose
- Add Behavioral Intervention
- Continue Behavioral Intervention
- Increase Behavioral Intervention
- Add Medication

Non-Responders
- Medication
- Behavioral Intervention

R

O1 ——— A1 ——— O2 / R Status ——— A2 ——— Y
Response/non-response at Week 8 is the primary tailoring variable.
There are 6 future or “second-line” treatment decisions

- Medication
  - Responders
  - Non-Responders
- Behavioral Intervention
  - Responders
  - Non-Responders

- Responders R
  - Continue Medication
  - Increase Medication Dose
  - Add Behavioral Intervention
  - Continue Behavioral Intervention
  - Increase Behavioral Intervention
  - Add Medication

O1 ――― A1 ――― O2 / R Status ――― A2 ――― Y
There are 4 embedded adaptive treatment strategies in this SMART; **Here is one**

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

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

**O1** → **A1** → **O2 / R Status** → **A2** → **Y**
There are 4 embedded adaptive treatment strategies in this SMART; **Here is another**

**Behavioral Intervention**
- Responders
- Non-Responders

**Medication**
- Responders
- Non-Responders

Continue Medication
- Increase Medication Dose
- Add Behavioral Intervention
- **Continue Behavioral Intervention**
- Increase Behavioral Intervention
- **Add Medication**

O1 ——— A1 ———— O2 / R Status ———— A2 ——— Y
Sequential randomizations ensure between treatment group balance.
A subset of the data arising from a SMART may look like this

<table>
<thead>
<tr>
<th>ID</th>
<th>ODD Dx</th>
<th>Baseline ADHD Score</th>
<th>Prior Med?</th>
<th>First Line Txt</th>
<th>Resp/Non-resp</th>
<th>Second Line Txt</th>
<th>School Perfm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.18</td>
<td>0</td>
<td>-1 MED</td>
<td>1</td>
<td>.</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-0.567</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>1 INTSFY</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.553</td>
<td>1</td>
<td>1 BMOD</td>
<td>0</td>
<td>-1 ADDO</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-0.013</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-0.571</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>-0.684</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>1.169</td>
<td>0</td>
<td>-1</td>
<td>1</td>
<td>.</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.369</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

This is simulated data.
Typical Primary Aim 1:
Main effect of first-line treatment?

• What is the best first-line treatment on average, controlling (by design) for future treatment?

• Among children with ADHD: Is it better on average, in terms of end of study mean school performance, to begin treatment with a behavioral intervention or with medication?
Primary Question 1 is simply a comparison of two groups!

**Medication**
- Responders
- Non-Responders

**Behavioral Intervention**
- Responders
- Non-Responders

**Decisions**
- Continue Medication
- Increase Medication Dose
- Add Behavioral Intervention
- Continue Behavioral Intervention
- Increase Behavioral Intervention
- Add Medication

O1 ——— A1 ———— O2 / R Status ———— A2 ——— Y
Primary Question 1 is simply a comparison of two groups

Mean end of study outcome for all participants initially assigned to Medication

Mean end of study outcome for all participants initially assigned to Behavioral Intervention

O1 —— A1 ———— O2 / R Status ———— A2 ——— Y
SAS code for a 2-group mean comparison in end of study outcome

* center covariates prior to regression;

data dat1;
    set libdat.fakedata;
    o11c = o11 - 0.2666667;
    o12c = o12 - -0.05561650;
    o13c = o13 - 0.2688887;
run;
* run regression to get between groups difference;
proc genmod data = dat1;
    model y = a1 o11c o12c o13c;
    estimate 'Mean Y under BMOD' intercept 1 a1 1;
    estimate 'Mean Y under MED' intercept 1 a1 -1;
    estimate 'Between groups difference' a1 2;
run;

This analysis is with simulated data.
The SAS code corresponds to a simple regression model

```
proc genmod data = dat1;
    model y = a1 o11c o12c o13c;
    estimate 'Mean Y under BMOD' intercept 1 a1 1;
    estimate 'Mean Y under MED' intercept 1 a1 -1;
    estimate 'Between groups difference' a1 2;
run;
```

The Regression Logic:

\[
Y = b0 + b1*A1 + b2*O11c + b3*O12c + b4*O13c + e
\]

Mean Y under BMOD = \( E( Y | A1=1 ) = b0 + b1*1 \)

Mean Y under MED = \( E( Y | A1=-1 ) = b0 + b1*(-1) \)

Between groups diff = \( E( Y | A1=1 ) - E( Y | A1=1 ) \)

= \( b0 + b1 - (b0 - b1) = 2*b1 \)
Primary Question 1 Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under BMOD</td>
<td>3.3443</td>
<td>3.1431</td>
<td>3.5436</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean Y under MED</td>
<td>3.2653</td>
<td>3.0469</td>
<td>3.4838</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Between groups diff</td>
<td>0.0780</td>
<td>-0.2229</td>
<td>0.3789</td>
<td>0.6115</td>
</tr>
</tbody>
</table>

In this simulated data set/experiment, there is no average effect of first-line treatment on school performance. Mean diff = 0.07 (p=0.6).

This analysis is with simulated data.
Or, here is the SAS code and results for the standard 2-sample t-test

```sas
data dat2; set dat1;
   if a1= 1 then altmp="BMOD";
   if a1=-1 then altmp="MED";
run;
proc ttest data=dat2;
   class altmp; var y;
run;
```

<table>
<thead>
<tr>
<th>altmp</th>
<th>N</th>
<th>Mean</th>
<th>Std Err</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMOD</td>
<td>82</td>
<td>3.2927</td>
<td>0.1090</td>
<td>-</td>
</tr>
<tr>
<td>MED</td>
<td>68</td>
<td>3.3088</td>
<td>0.1053</td>
<td>-</td>
</tr>
<tr>
<td>Diff (BMOD-MED)</td>
<td>-0.0161</td>
<td>0.1534</td>
<td>0.91</td>
<td></td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Side Analysis: Impact of first-line treatment on early non/response rate
Side analysis: SAS code and results for “myopic effect” of first-line treatment

```sas
proc freq data=dat1;
  table a1*r / chisq nocol nopercent;
run;
```

<table>
<thead>
<tr>
<th>Frequency</th>
<th>R = 0</th>
<th>R = 1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row Pct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1 = -1</td>
<td>34</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>MED</td>
<td>50.00</td>
<td>50.00</td>
<td></td>
</tr>
<tr>
<td>A1 = 1</td>
<td>55</td>
<td>27</td>
<td>82</td>
</tr>
<tr>
<td>BMOD</td>
<td>67.07</td>
<td>32.93</td>
<td></td>
</tr>
</tbody>
</table>

This analysis is with simulated data.

In terms of early non/response rate, initial MED is better than Initial BMOD by 17% (p-value = 0.03).
Typical Primary Question 2: Best of two adaptive interventions?

• In terms of average school performance, which is the best of the following two ATS:

  First treat with medication, then
  • If respond, then continue treating with medication
  • If non-response, then add behavioral intervention

  versus

  First treat with behavioral intervention, then
  • If response, then continue behavioral intervention
  • If non-response, then add medication
Comparison of mean outcome had population followed the red ATS versus...

Medication

Responders

Non-Responders

Behavioral Intervention

Responders

Non-Responders

Continue Medication

Increase Medication Dose

Add Behavioral Intervention

Continue Behavioral Intervention

Increase Behavioral Intervention

Add Medication

O1 ——— A1 ———— O2 / R Status ———— A2 ——— Y
...versus the mean outcome had all population followed the blue ATS
But we cannot compare mean outcomes for participants in red versus those in blue.
There is imbalance in the non/responding participants following the red ATS...

...because, by design,

- Responders to MED had a $0.5 = 1/2$ chance of having had followed the red ATS, whereas
- Non-responders to MED only had a $0.5 \times 0.5 = 0.25 = 1/4$ chance of having had followed the red ATS
To estimate mean school performance had all participants followed the red ATS:

- Assign $W = \text{weight} = 2$ to responders to MED
- Assign $W = \text{weight} = 4$ to non-responders to MED
- Take $W$-weighted mean of sample who followed red ATS
SAS code to estimate mean outcome had all participants followed red ATS

* create indicator and assign weights;

```
data dat3; set dat2;
    Z1=-1;
    if A1*R=-1 then Z1=1; if (1-A1)*(1-R)*A2=-2 then Z1=1;
    W=4*R + 2*(1-R);
run;
```

* run W-weighted regression Y = b0 + b1*z1 + e; * b0 + b1 will represent the mean outcome under red ATS;
```
proc genmod data = dat3;
    class id;
    model y = z1;
    scwgt w;
    repeated subject = id / type = ind;
    estimate 'Mean Y under red ATS' intercept 1 z1 1;
run;
```

Request robust standard errors: Why? Weights depend on responder status, which is unknown ahead of time.

This analysis is with simulated data.
Results: Estimate of mean outcome had population followed red ATS

Analysis Of GEE Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SError</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.2913</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Z1</td>
<td>-0.0481</td>
<td>0.5435</td>
</tr>
</tbody>
</table>

Contrast Estimate Results

<table>
<thead>
<tr>
<th>95% Conf Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate Lower</td>
</tr>
<tr>
<td>Upper SError</td>
</tr>
</tbody>
</table>

Mean Y under the red ATS

| 3.2432 | 3.0262 | 3.4602 | 0.1107 |

This analysis is with simulated data.
Similarly calculate the mean outcome had all participants followed the blue ATS

\[ O_1 \rightarrow A_1 \rightarrow O_2 / R \text{ Status} \rightarrow A_2 \rightarrow Y \]
SAS code to estimate mean outcome had all participants followed blue ATS

* create indicator and assign weights;
data dat4; set dat2;
  Z2=-1;
  if A1*R= 1 then Z2=1; if (1+A1)*(1-R)*A2=-2 then Z2=1;
  W=4*R + 2*(1-R);
run;
* run W-weighted regression Y = b0 + b1*z2 + e;
* b0 + b1 will represent the mean outcome under blue ATS;
proc genmod data = dat4;
  class id;
  model y = z2;
  scwgt w;
  repeated subject = id / type = ind;
  estimate 'Mean Y under blue ATS' intercept 1 z2 1;
run;

This analysis is with simulated data.
Results: Estimate of mean outcome had population followed red ATS

Analysis Of GEE Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SError</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.3485</td>
<td>0.0867</td>
</tr>
<tr>
<td>Z2</td>
<td>0.1206</td>
<td>0.0867</td>
</tr>
</tbody>
</table>

Contrast Estimate Results

<table>
<thead>
<tr>
<th>95% Conf Limits</th>
<th>Estimate Lower</th>
<th>Upper</th>
<th>SError</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under the blue ATS</td>
<td>3.4691</td>
<td>3.2020</td>
<td>3.7363</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
What about a regression that allows us to compare the red and the blue ATS?
SAS code for a weighted regression to analyze Primary Question 2

data dat5; set dat2;
  Z1=-1; Z2=-1; W=4*R + 2*(1-R);
  if A1*R=-1 then Z1=1; if (1-A1)*(1-R)*A2=-2 then Z1=1;
  if A1*R= 1 then Z2=1; if (1+A1)*(1-R)*A2=-2 then Z2=1;
run;

data dat6; set dat5; if Z1=1 or Z2=1 run;
proc genmod data = dat6;
  class id;
  model y = z1;
  scwgt w;
  repeated subject = id / type = ind;
  estimate 'Mean Y under red ATS' intercept 1 z1  1;
  estimate 'Mean Y under blue ATS' intercept 1 z1 -1;
  estimate '     Diff: red - blue' z1  2;
run;

A key step: This regression should be done only with the participants following the red and blue ATs.

This analysis is with simulated data.
Primary Question 2 Results

Analysis Of GEE Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SError</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.3562</td>
<td>0.0878</td>
</tr>
<tr>
<td>Z2</td>
<td>-0.1129</td>
<td>0.0878</td>
</tr>
</tbody>
</table>

Contrast Estimate Results

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>SError</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under red ATS</td>
<td>3.2432</td>
<td>3.0262</td>
<td>3.4602</td>
</tr>
<tr>
<td>Mean Y under blue ATS</td>
<td>3.4691</td>
<td>3.2020</td>
<td>3.7363</td>
</tr>
<tr>
<td>Diff: red - blue</td>
<td>-0.2259</td>
<td>-0.5701</td>
<td>0.1183</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Let’s take a quick break!
What about a regression that allows comparison of mean under all four ATSs?
What about a regression that allows comparison of mean under all four ATSs?
SAS code for the regression to compare means under all four ATSSs

```sas
data dat7; set dat2;
  * define weights and create responders replicates
  * (with equal "probability of getting A2");
  if R=1 then do;
    ob = 1; A2 = -1; weight = 2; output;
    ob = 2; A2 = 1; weight = 2; output;
  end;
  else if R=0 then do;
    ob = 1; weight = 4; output;
  end;
run;
```

This analysis is with simulated data.
Working intuition about replication step: undo weighting for certain comparisons

- Behavioral Intervention
  - Responders
  - Non-Responders
  - versus

- Behavioral Intervention
  - Responders
  - Non-Responders
  - versus

- Continue Behavioral Intervention
  - Add Medication
  - Continue Behavioral Intervention
  - Increase Behavioral Intervention
SAS code for a weighted regression to estimate mean under all four ATSS

```sas
proc genmod data = dat7;
   class id;
   model y = a1 a2 a1*a2;
   scwgt weight;
   repeated subject = id / type = ind;
   estimate 'Mean Y under red ATS' int 1 a1 -1 a2 -1 a1*a2 1;
   estimate 'Mean Y under blue ATS' int 1 a1 1 a2 -1 a1*a2 -1;
   estimate 'Mean Y under green ATS' int 1 a1 -1 a2 1 a1*a2 -1;
   estimate 'Mean Y under orange ATS' int 1 a1 1 a2 1 a1*a2 1;
   estimate '    Diff: red - blue' int 0 a1 -2 a2 0 a1*a2 0;
   estimate '    Diff: orange - blue' int 0 a1 0 a2 2 a1*a2 2;
   estimate '    Diff: green - blue' int 0 a1 -2 a2 2 a1*a2 0;
* etc...;
run;
```

This analysis is with simulated data.
Results: weighted regression method to estimate mean outcome under all 4 ATTs

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under red ATS</td>
<td>3.2432</td>
<td>3.0262</td>
<td>3.4602</td>
</tr>
<tr>
<td>Mean Y under blue ATS</td>
<td>3.4691</td>
<td>3.2020</td>
<td>3.7363</td>
</tr>
<tr>
<td>Mean Y under green ATS</td>
<td>3.3871</td>
<td>3.0830</td>
<td>3.6912</td>
</tr>
<tr>
<td>Mean Y under orange ATS</td>
<td>3.1205</td>
<td>2.8264</td>
<td>3.4146</td>
</tr>
<tr>
<td>Diff: red - blue</td>
<td>0.0204</td>
<td>-0.2737</td>
<td>0.3144</td>
</tr>
<tr>
<td>Diff: orange - blue</td>
<td>-0.3487</td>
<td>-0.7271</td>
<td>0.0298</td>
</tr>
<tr>
<td>Diff: green - blue</td>
<td>-0.0820</td>
<td>-0.4868</td>
<td>0.3227</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
SAS code for a wtd. regression to estimate mean under all four ATSSs **with more power**

```sas
proc genmod data = dat7;
  class id;
  model y = a1 a2 a1*a2 o11 o12 o13;
  scwgt weight;
  repeated subject = id / type = ind;
  estimate 'Mean Y under red ATS' int 1 a1 -1 a2 -1 a1*a2 1;
  estimate 'Mean Y under blue ATS' int 1 a1 1 a2 -1 a1*a2 -1;
  estimate 'Mean Y under green ATS' int 1 a1 -1 a2 1 a1*a2 -1;
  estimate 'Mean Y under orange ATS' int 1 a1 1 a2 1 a1*a2 1;
  estimate 'Diff: red - blue'   a1  -2  a2   0  a1*a2  0;
  estimate 'Diff: orange - blue' int 0 a1 0 a2 2 a1*a2 2;
  estimate 'Diff: green - blue' int 0 a1 -2 a2 2 a1*a2 0;
* etc...;
run;
```

**Improve efficiency:** Adjusting for baseline covariates that are associated with outcome leads to more efficient estimates (lower standard error = more power = smaller p-value).

This analysis is with simulated data.
### Results: more powerful wtd. Regression to estimate mean outcome under all 4 ATSs

**Improved efficiency:**
Adjusting for baseline covariates resulted in smaller standard error. Point estimates remained the same, as expected.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under red ATS</td>
<td>3.2025</td>
<td>2.9493</td>
<td>3.4557</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under blue ATS</td>
<td>3.5229</td>
<td>3.2851</td>
<td>3.7607</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under green ATS</td>
<td>3.3392</td>
<td>3.0040</td>
<td>3.6744</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under orange ATS</td>
<td>3.1692</td>
<td>2.9020</td>
<td>3.4365</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Diff:**
- red - blue               -0.0752  -0.3960  0.2455  0.6458
- orange - blue             -0.3537  -0.6915  -0.0158  0.0402
- green - blue              -0.1837  -0.6056  0.2381  0.3933

This analysis is with simulated data.
Summary of Primary Aims
Data Analysis

• The blue ATS led to the largest estimated mean school performance (mean = 3.5229):

  - Behavioral Intervention
  - Responders
  - Non-Responders
  - Continue Behavioral Intervention
  - Add Medication

• Despite MED initially having stronger early response rate (17% over BMOD initially), the best ATS begins with BMOD!

This analysis is with simulated data.
Citations

Exercise: Using the sample SMART you developed previously, write down a primary research question of interest to you. What data analysis approach would you use to address this question?

Next up: Secondary Aims Using Data Arising from a SMART
Secondary Aims Using Data Arising from a SMART

Getting SMART About Developing Individualized Sequences of Health Interventions

University of Minnesota, NIMH Prevention Center, June 8

Daniel Almirall & Susan A. Murphy
Secondary Analyses Outline

- Auxiliary data typically in a SMART used for secondary aims?
- Typical secondary research questions (aims) in a SMART
- SAS code snippets
- Results from worked examples
  - All analyses are with simulated data!
Other Measures Collected in a SMART

**O1** A1 **O2** / R Status **A2** Y

- Medication
  - Responders
  - Non-Responders

- Behavioral Intervention
  - Responders
  - Non-Responders

**O1** = Demog., Pre-txt Medication Hx, Pre-txt ADHD scores, Pre-txt school performance, ODD Dx, ...

**O2** = Month of non-response, adherence to first-stage txt, ...

- Continue Medication
- Increase Medication Dose
- Add Behavioral Intervention
- Continue Behavioral Intervention
- Increase Behavioral Intervention
- Add Medication
Typical Secondary Aim 1: Best second-line tactic?

• Among children who do not respond to (either) first-line treatment, is it better to increase initial treatment or to add a different treatment to the initial treatment?
Typical Secondary Aim 1: Best second-line tactic?

- **Medication**
  - Responders
  - Non-Responders
  - Behavioral Intervention

- **Behavioral Intervention**
  - Responders
  - Non-Responders

- **Medication**
  - Increase Medication Dose
  - Add Behavioral Intervention
  - Increase Behavioral Intervention
  - Add Medication

O1 ——— A1 ———— O2 / R Status ———— A2 ——— Y
SAS code and results for
Secondary Aim 1: Second-line tactic

* use only non-responders;
data dat4;
   set dat1; if R=0;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat4;
   model y = a2 o11c o12c o13c;
estimate 'Mean Y w/INTENSIFY tactic' intercept 1 a2 1;
estimate 'Mean Y w/ADD TXT tactic' intercept 1 a2 -1;
estimate 'Between groups difference' a2 2;
run;

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y w/INTENSIFY tactic</td>
<td>3.2143</td>
<td>2.9026</td>
<td>3.5260</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean Y w/ADD TXT tactic</td>
<td>3.4255</td>
<td>3.1308</td>
<td>3.7202</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Between groups difference</td>
<td>-0.2112</td>
<td>-0.6402</td>
<td>0.2177</td>
<td>0.3345</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Typical Secondary Aim 2:
Best second-line treatment?

a. Among children who do not respond to first-line medication, is it better to increase dosage or to add behavioral modification?

b. Among children who do not respond to first-line behavioral modification, is it better to increase intensity of behavioral treatment or to add medication?
Typical Secondary Aim 2: Best second-line treatment?

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

O1 ——— A1 ———— O2 / R Status ———— A2 ——— Y
SAS code and results for Secondary Aim 2a: Second-line txt after MED

* use only medication non-responders;
data dat2;
   set dat1; if R=0 and A1=-1;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat2;
   model y = a2 ;
   estimate 'Mean Y w/INTENSIFY MED' intercept 1 a2  1;
   estimate 'Mean Y w/ADD BMOD'      intercept 1 a2 -1;
   estimate 'Between groups difference'          a2  2;
run;

Contrast Estimate Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y w/INTENSIFY MED</td>
<td>3.5714</td>
<td>3.0862</td>
<td>4.0567</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean Y w/ADD BMOD</td>
<td>3.2500</td>
<td>2.8440</td>
<td>3.6560</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Between groups difference</td>
<td>0.3214</td>
<td>-0.3113</td>
<td>0.9541</td>
<td>0.3194</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
SAS code and results for Secondary Aim 2b: Second-line txt after BMOD

* use only BMOD non-responders;
data dat3;
  set dat1; if R=0 and A1=1;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat3;
  model y = a2 o11c o12c o13c;
estimate 'Mean Y w/INTENSIFY BMOD' intercept 1 a2  1;
estimate 'Mean Y w/ADD MED'        intercept 1 a2 -1;
estimate 'Between groups difference'           a2  2;
run;

Contrast Estimate Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y w/INTENSIFY BMOD</td>
<td>3.0357</td>
<td>2.6436</td>
<td>3.4278</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean Y w/ADD MED</td>
<td>3.5556</td>
<td>3.1563</td>
<td>3.9548</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Between groups difference</td>
<td>-0.5198</td>
<td>-1.0795</td>
<td>0.0398</td>
<td>0.0687</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Typical Secondary Aim 3: Second-line treatment tailoring?

a. Does adherence to first-line MED strongly moderate the impact of increasing MED dosage versus adding BMOD?

b. Does adherence to first-line BMOD strongly moderate the impact of intensifying BMOD versus adding MED?
Typical Secondary Aim 3: Second-line treatment tailoring?

- Medication
  - Responders
  - Non-Responders
  - Adherence to initial MED

- Behavioral Intervention
  - Responders
  - Non-Responders
  - Adherence to initial BMOD

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

O1 — A1 —- O2 / R Status —- A2 —- Y
SAS code and results for Secondary Aim 3:
Second-line treatment tailoring

* use only non-responders;
data dat5; set dat1; if R=0; run;

* comparison of add vs intensify given first line txt and adherence;
proc genmod data = dat5;
  model y = o11c o12c o13c a1 a1*o11c o21c o22 a2 a2*a1 a2*o22;
  * effect of add vs intensify given first-line = MED x ADH status;
  estimate 'INT vs ADD for NR MED ADH' a2 2 a2*a1 -2 a2*o22 2 ;
  estimate 'INT vs ADD for NR MED Non-ADH' a2 2 a2*a1 -2 a2*o22 0 ;
  * effect of add vs intensify given first-line = BMOD x ADH status;
  estimate 'INT vs ADD for NR BMOD ADH' a2 2 a2*a1 2 a2*o22 2 ;
  estimate 'INT vs ADD for NR BMOD Non-ADH' a2 2 a2*a1 2 a2*o22 0 ;
run;

Contrast Estimate Results

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT vs ADD for NR MED ADH</td>
<td>1.0473</td>
<td>0.5682</td>
<td>1.5263</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>INT vs ADD for NR MED Non-ADH</td>
<td>-1.5658</td>
<td>-2.1587</td>
<td>-0.9728</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>INT vs ADD for NR BMOD ADH</td>
<td>1.2651</td>
<td>0.7529</td>
<td>1.7773</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>INT vs ADD for NR BMOD Non-ADH</td>
<td>-1.3479</td>
<td>-1.7493</td>
<td>-0.9465</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Side analysis: SAS code and results for impact of first-line treatment on ADH

```sas
proc freq data=dat1;
    table a1*o22 / chisq nocol nopercent;
run;
```

In terms of adherence, initial MED is better than initial BMOD by 22% (p-value < 0.01).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>ADH = 0</th>
<th>ADH = 1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1 = -1</td>
<td>28</td>
<td>40</td>
<td>68</td>
</tr>
<tr>
<td>MED</td>
<td>41.18</td>
<td>58.82</td>
<td></td>
</tr>
<tr>
<td>A1 = 1</td>
<td>52</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>BMOD</td>
<td>63.41</td>
<td>36.59</td>
<td></td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
Let’s take a quick break!

Up next: A method for building a more deeply tailored ATS.
Typical Secondary Aim 4: A more deeply individualized ATS via Q-learning

Q-Learning is an extension of regression to sequential treatments.

• Q-Learning results in a proposal for an adaptive treatment strategy with greater individualization.
• A subsequent trial would evaluate the proposed adaptive treatment strategy versus usual care.
Steps in Q-Learning Regression

*Work backwards (reverse-engineering!)*

1. Do a regression to learn about more deeply individualizing second-line treatment
   - Assign each non-responder the value $\hat{Y}_i$, an estimate of the outcome under the second-line treatment that yields best outcome. Responders get observed $Y_i$.

2. Using $\hat{Y}_i$ do a regression to learn about more deeply individualizing first-line treatment

**Step 1: Note, We already did this for Aim 3!**
Q-Learning Step 1: Learn optimal second-line treatment for non-responders

Among non-adherers to either first-line treatment, better to augment.

\[ \text{INT} - \text{ADD} \approx -1.4 \]

This analysis is with simulated data.
Q-Learning Step 1: Learn optimal second-line treatment for non-responders

Among adherers to either first-line treatment, better to intensify first-line txt.

This analysis is with simulated data.
Q-Learning Step 2: Learn optimal first-treatment for all given optimal future txt

Among kids using MED in prior year, it is better to start with MED.

This analysis is with simulated data.
Q-Learning Step 2: Learn optimal first-treatment for all given optimal future txt

Among kids not using MED in prior year, it is better to start with BMOD

This analysis is with simulated data.
What did we learn with Q-learning?

*Adaptive Treatment Strategy Proposal*

- If the child used MED in prior year, then begin with MED; otherwise, begin with BMOD.

- If the child is non-responsive and non-adherent to either first-line treatment, then AUGMENT with the other treatment option.

- If the child is non-responsive but adherent to either first-line treatment, then it is better to INTENSIFY first-line treatment.

- If the child is responsive to first-line treatment, then CONTINUE first-line treatment.

This Q-learning analysis was done with simulated/altered data.
What did we learn with Q-learning?

Adaptive Treatment Strategy Proposal

• The mean Y, school performance, under the more deeply individualized ATS obtained via Q-learning is estimated to be 3.99.

• This is larger than the value of the ATS which started with BMOD and augmented with MED for non-responders (mean = 3.47)

• (BMOD, MED) was the ATS with the largest mean among the 4 embedded ATSs.

This Q-learning analysis was done with simulated/altered data.
Citations


Exercise: Using the sample SMART you developed previously, write down a secondary research question of interest to you. What data analysis approach would you use to address this question?
Thank you.

• Software for Q-learning is now available in R and it is coming out soon for SAS! Visit: methodology.psu.edu/ra/adap-treat-strat/qlearning

• These slides will be posted at www-personal.umich.edu/~dalmiral/