Sequential, Multiple Assignment, Randomized Trials

Getting SMART About Developing Individualized Sequences of Adaptive Health Interventions

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50 minutes
Sequential Multiple Assignment Randomized Trials (SMARTs)?
Why do we need SMARTs?
Give ADHD example SMART.
What are typical primary and secondary questions?
Discuss standard SMART design principles.
Briefly discuss sample size issues in this context. De-bunk misconception that SMARTs necessarily require large sample sizes.
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.*

Take a broad view of what constitutes therapies: changing intensity, switching medication, augmenting medication, behavioral contingencies, monitoring schedules, motivational therapy, support networks, form of treatment delivery.
Outline

• What are Sequential Multiple Assignment Randomized 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.*

In stat. people may call these multistage trials (the randomization at each stage is assumed)
Hypothetical trial: Outcome is not shown but is on far right. The randomizations can take place up front.

Equal randomization

Usual reaction is (1) I’m worried about sample size and (2) This looks awfully complicated.
In reality both of these problems are less worrisome than one might think—see following slides.
An adaptive treatment strategy is indicated in blue
Outline

- What are Sequential Multiple Assignment Trials (SMARTs)?
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Challenges in constructing Adaptive Treatment Strategies

• Delayed, Prescriptive & Sample Selection Effects
  --- *sequential multiple assignment randomized trials (SMART)*

• Adaptive Treatment Strategies are Multi-component Treatments
  --- *series of screening/refining randomized trials prior to confirmatory trial (MOST)*.

Particularly attractive since potential initial treatment may have been evaluated in prior trials. So you propose a responder study or you propose a nonresponder study.

Or, why choosing the best initial treatment on the basis of a randomized trial of initial treatments and choosing the best secondary treatment on the basis of a randomized trial of secondary treatments is not the best way to construct an adaptive treatment strategy.
counseling and then if respond, monitoring with low level telephone counseling.

A consequence is that comparing two initial therapies based on a proximal outcome may produce different results from the comparison of two initial therapies when followed by a particular maintenance therapy and comparing more distal outcomes. Additionally, restricting comparisons to longer term outcomes, a comparison of two initial therapies followed by usual care or no therapy may yield different results from the comparison of two initial therapies when followed by one of several maintenance therapies.

We can expect that in an optimized adaptive treatment strategies, the best subsequent therapy will build on the gains achieved by prior therapies and thus these delayed effects should be common.

We want big positive delayed effects. We want profound positive cross-over effects!!!
treatment of psychosis: a medication may result in many immediate responders but
Some patients are not helped and/or experience abnormal movements of the voluntary muscles (TDs). The class of subsequent medications is greatly reduced.

Or the kind of response produced may not be sufficiently strong so that patients can take advantage of maintenance care.

A negative delayed effect would occur if the initial treatment overburdens an individual, resulting decreased responsivity to future treatment; see Thall et al. (2007), Bembom and van der Laan (2007) for an example of the latter in cancer research.
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.

Consider the issue of motivation as expressed via adherence: if tx A has provides less adherence support than tx B, then patients who require the adherence support will exhibit adherence problems during tx with A but not during tx with B. This is useful information as we then know that these patients, even if they respond will potentially need an enhancement of an adherence support during the maintenance or aftercare phase.
Consider the issue of adherence; in many historical trials subjects were assigned a fixed treatment, that is, there were no options besides non-adherence for subjects who were not improving. This often leads to higher than expected drop-out or non-adherence. This is particularly the case in longer studies where continuing treatments that are ineffective is likely associated with high non-adherence. As a result the subjects who remained in the historical trial may be quite different from the subjects that remain in a SMART trial, which by design provides alternates for non-improving subjects. David Oslin made this point to me.

Consider the issue of motivation. Nonresponder trials recruit individuals who are not responding to their present treatment, say Med A. An important consideration is whether these nonresponders represent the population of individuals who do not respond to Med A or whether the nonresponders recruited into the trial are more motivated. Such selection bias will prevent us from realizing that we might need a behavioral intervention to encourage nonresponders to start again with treatment.
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.

Just because an initial txt looks best when looking at intermediate outcomes does not mean that it is best in an adaptive txt strategy.
Don’t know why your treatment strategy worked or did not work. Did not open black box. Should we wait until patient has had 5 heavy drinking days before giving up on this medication or should we give up on this medication after only 2 heavy drinking days?

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 an adaptive treatment strategy and then comparing the strategy 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.

confirmatory trial is to compare the developed adaptive treatment strategy versus an appropriate alternative—this is the standard randomized two group trial.

MOST multistage optimization strategy
Hypothetical trial: Outcome is not shown but is on far right. The randomizations can take place up front.

Equal randomization

Usual reaction is (1) I’m worried about sample size and (2) This looks awfully complicated.

In reality both of these problems are less worrisome than one might think—see following slides.
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

The primary analyses are being conducted with the second two
Outline

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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.

Note we considered different txt’s for the responders as compared to the nonresponders.
SMART Design Principles

• Choose primary hypotheses that are both scientifically important and aid 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.

These are main effects *a la’* ANOVA

The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

Example 1: Effects of secondary treatments are controlled by experimental design –not by statistical analysis
A study of initial tx’s in which subsequent tx’s are controlled.
Here you can use a variety of analyses, growth curve models, survival analysis, etc.
A study of nonresponders in which one controls the tx’s to which people don’t respond to.
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.*

These are main effects a la’ ANOVA
Sigma for example 1 is the std of primary outcome of patients initially assigned tx A (or B)

Sigma for example 2 is the std of primary outcome of non-responding patients who are assigned a switch (or augment)

Throughout working assumptions are equal variances and normality

Sample sizes calculated on the website:
http://hedwig.mgh.harvard.edu/sample_size/quan_measur/para_quant.html

<table>
<thead>
<tr>
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<th>Example 1</th>
<th>Example 2</th>
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<tbody>
<tr>
<td>$\frac{\Delta \mu}{\sigma} = .3$</td>
<td>$N = 402$</td>
<td>$N = 402$/initial nonresponse rate</td>
</tr>
<tr>
<td>$\frac{\Delta \mu}{\sigma} = .5$</td>
<td>$N = 146$</td>
<td>$N = 146$/initial nonresponse rate</td>
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$\alpha = .05$, power $= 1 - \beta = .85$
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).

Confounding::: alternative explanations other than txt effect for the observed comparisons
Use analysis of covariance or regression.
Just use nonresponders’ data. For example with a continuous outcome we might use a regression that includes an interaction term between second stage treatment and adherence.
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Pop’n: children who are nonverbal (not using spoken language) by 5 years of age despite involvement in traditional intervention programs

N=90  6 month trial

cutoff for nonresponse at 12 weeks (three measures of communication to yield our response/non-response indicator: number of words used spontaneously during parent-child interaction, number of communicative functions used for each word during parent-child interactions, and generalization of spontaneous words to express multiple communication functions.) Responder status—increase of 25% over baseline in at least half of 14 assessment measures

JAE Joint attention and joint engagement

Enhanced Milieu Teaching (EMT) is a naturalistic language intervention that promotes functional use of new language forms in the context of every
day interactions with parents and teachers. EMT uses environmental arrangement, responsive interaction, language modeling, and systematic prompting procedures to teach functional language.

augmentative and alternative communication interventions (AAC)

Primary Aim:
1) To compare the slopes in outcome measures of communication and language across three time periods (times 0, 3 months and 6 months) for the two treatments: JAE + AAC strategy vs enhanced JAE strategy
We are analyzing this data

The medication is Ritalin

Adaptive Pharmacological and Behavioral Treatments for Children with ADHD: Sequencing, Combining, and Escalating Doses

(1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND

(2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

Primary outcome is measure of child behavior at 8 months. N=153
This study is in the field, \( n=300 \) primary hypothesis compared always traditional RBT vs always reduce RBT

Primary outcome is “in treatment when child born”

Nonresponse == missed unexcused tx day or positive urine for opioid or cocaine use or self report of opioid/cocaine use

RBT==reinforcement based tx

These differ in intensity and scope (in increasing order below)

aRBT is abbreviated RBT
rRBT is reduced RBT
tRBT is traditional
eRBT is enhanced
Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist then in ensuing two months are monitored for heavy drinking
N=302 sized to detect the contrast between two alternatives for non-responders primary outcome (drinking behavior from the TLFB)

Trigger for nonresponse is heavy drinking days
Early trigger 2 or more hdd
Late trigger 5 or more hdd
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


Very technical:

Practice Exercise

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

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