

Getting SMART about Developing Individualized, Adaptive Health Interventions: An Introduction to a Novel Experimental Study Design

6th Annual Advanced Training Institute on Health Behavior Theory
Madison, Wisconsin – Thursday, July 19, 8:00AM-10:30AM

Instructor: Daniel Almirall & Susan A. Murphy (University of Michigan)

Module	Time	Topic
MODULE 1	08:00-8:45AM (45 min)	Introduction to Adaptive Health Interventions <ul style="list-style-type: none"> • What are adaptive health interventions (AHI)? • What are the pieces that make up an AHI? • Compare simple versus deeply-tailored AHIs. • Discuss why AHIs are needed • Utilizing theory to design an AHI • How AHIs can be used to inform clinical practice
PRACTICUM/Q&A	8:45-9:15AM (30 min)	Practice Exercise & Continued Discussion <i>Exercise:</i> Write/draw a simple (2 critical decision-point) AHI involving addressing a chronic disorder in your field. <i>Discussion Question:</i> How are AHIs similar and different from the types of behavioral interventions we typically think about?
MODULE 2	9:15-10:00AM (45 min)	Sequential Multiple Assignment Randomized Trials (SMARTs) <ul style="list-style-type: none"> • What are SMARTs? • Why do we need SMARTs? • Discuss SMART design principles. • What are typical primary and secondary aims in a SMART? • How do SMART designs differ from standard randomized clinical trial designs? • Give examples of SMARTs used to develop AHIs, that are completed or currently in the field: <ul style="list-style-type: none"> ○ Prostate cancer (a useful SMART precursor to discuss), autism, child ADHD, women who are pregnant and abuse substances, adult alcohol use
PRACTICUM/Q&A	10:00-10:30AM (30 min)	Practice Exercise and Continued Discussion <i>Exercise:</i> Begin thinking about a SMART design in your research. What would the first randomization be? Second randomization? How can you incorporate the AHI you developed in Module 1 into this design? <i>Discussion Question:</i> What is the primary purpose of a SMART? How are SMARTs different from standard RCTs?

List of References for Adaptive Health Interventions and SMART

L.M Collins, S.A. Murphy and K.A. Bierman (2004), A Conceptual Framework for Adaptive Preventive Interventions, *Prevention Science* 5:185-196.

S.A. Murphy & J.R. McKay (2004), Adaptive Treatment Strategies: an Emerging Approach for Improving Treatment Effectiveness. *Clinical Science (Newsletter of the American Psychological Association Division 12, section III: The Society for the Science of Clinical Psychology)* Winter 2003/Spring 2004

L.M. Collins, S.A. Murphy, V. Nair & V. Strecher (2005), A Strategy for Optimizing and Evaluating Behavioral Interventions, *Annals of Behavioral Medicine*. 30:65-73.

S.A. Murphy, L.M. Collins, A.J. Rush (2007). Customizing Treatment to the Patient: Adaptive Treatment Strategies. *Drug and Alcohol Dependence*, 88(2):S1-S72.

S.A. Murphy, K.G. Lynch, J.R. McKay, D. Oslin, T. TenHave (2007). Developing Adaptive Treatment Strategies in Substance Abuse Research. *Drug and Alcohol Dependence*, 88(2):S24-S30

L.M. Collins, S.A. Murphy, V. Strecher (2007). The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent e-Health Interventions. *American Journal of Preventive Medicine*, 32(5S):S112-118

A.I. Oetting, J.A. Levy, R.D. Weiss, S.A. Murphy (2011), Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies,, *Causality and Psychopathology: Finding the Determinants of Disorders and their Cures*, (P.E. Shrout, K.M. Keyes, K. Ornstein, Eds.) Arlington VA: American Psychiatric Publishing, Inc, pgs. 179-205

H. Lei, I. Nahum-Shani, K. Lynch, D. Oslin and S.A. Murphy. A SMART Design for Building Individualized Treatment Sequences, *The Annual Review of Clinical Psychology (2012)*, Vol. 8: 21-48

I. Nahum-Shani, M. Qian, D. Almirall, W. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2012; in press). Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. *Psychological Methods*. *To appear: Meanwhile, obtain a copy of an older Technical Report from the Methodology Center at Penn State University.*

Almirall D., Compton S.N., Gunlicks-Stoessel M., Duan N., Murphy S.A. (accepted 2011; to appear). *Preparing for a Sequential Multiple Assignment Randomized Trial for Developing an Adaptive Treatment Strategy: Designing a SMART Pilot Study*. *Statistics in Medicine*, Vol 31, No. 17. *To appear: Meanwhile, obtain a copy of an older Technical Report from the Methodology Center at Penn State University.*

Almirall D., Compton S.N., Rynn M.A., Walkup J.T., Murphy S.A. (accepted 2012; in press). *SMARTer Discontinuation Trials: With Application to the Treatment of Anxious Youth*. *Journal of Child and Adolescent Psychopharmacology*. *To appear: Meanwhile, obtain a copy of an older Technical Report from the Methodology Center at Penn State University.*

Adaptive Health Interventions

Module 1

Getting SMART About Developing Individualized Adaptive Health Interventions

6th Annual Advanced Training Institute on Health
Behavior Theory, Madison, Wisconsin, July 19
Daniel Almirall & Susan A. Murphy



45 minutes

Introduction to Adaptive Health Interventions

What are Adaptive Health Interventions (AHI)?

What are the pieces that make up an AHI?

Examples of AHIs: Compare simple versus deeply-tailored AHIs.

Discuss why AHIs are needed

Utilizing theory to design an AHI

How AHIs can be used to inform clinical practice

Before We Begin...Throughout This
Module, Keep in Mind the End-of-
Module Practice Exercise and Discussion
Question

Exercise: *Write/draw one simple AHI to address
a disorder in your field.*

Discussion Question: *How are AHIs
similar/different to the types of behavioral
interventions we typically think about?*

Outline

- What are Adaptive Health Interventions?
- Why use Adaptive Health Interventions?
- Adaptive Health Intervention Design Goals
- What does an Adaptive Health Intervention include?
- Summary & Discussion

Other names are:

adaptive treatment strategies (ATS; this is very common in the mental health literature), dynamic treatment regimes (in the bio/statistical literature, this is very common), treatment algorithms (in psychiatry), stepped care models, expert systems, adaptive interventions, treatment protocols. Structured treatment interruptions in the treatment of AIDS are a form of adaptive txt strategy.

Individualized interventions is another name

Adaptive Health Interventions

- 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.

Provide a paradigm whereby we can seek to improve clinical practice which by its nature is adaptive.

Tailoring is achieved by use of a decision rules. Takes ongoing info (past response, adherence, burden,etc) and outputs txt level type

Scientists develop AHIs first. They are then used by clinicians to guide their thinking in actual clinical practice.

We use the term AHI but others might use the terms: dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols.

Example: Adaptive Aftercare for Alcohol Dependent Individuals

- **Population:** alcohol dependent individuals who have graduated from an intensive outpatient program
- **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

All alcohol dependent individuals are provided Naltrexone along with Medical Management upon graduation.

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.

Individuals have weekly medical management visits

naltrexone medication (opiate antagonist—reduces the reinforcing or pleasurable effects of alcohol)
+ MM is standard treatment

CBI is combine behavioral intervention this is motivational enhancement and cognitive behavioral therapy—incorporates pharmacotherapy

Adaptive Health Interventions

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

- How long should we use the first treatment before transitioning to a maintenance/relapse prevention treatment? And which treatment should this be?
- How long should we try the first treatment before declaring non-response and moving to another treatment? And which treatment should this be?
- How should a treatment be delivered?
- How do we re-engage patients who are non-adherent?

Other critical decisions: The individual's participation in treatment (e.g., who should set health-related goals, the participant or the care provider?), the location of the intervention offered (e.g., is it better to offer treatment at home or at the clinic?), the provider of the intervention (e.g., should the parent or the teacher intervene?), the mode of delivery (e.g., is face-to-face delivery better than Internet-based delivery?), or the timing of treatment (e.g., is it better to intervene immediately or at some later point?)

More examples of tailoring variables

- Age, Severity of illness, Presence of comorbid mental or physical conditions, Quality of family support, Past failed treatments
- Adherence to present treatment, Side effects while on present treatment, Symptoms while on present treatment
- Candidate tailoring variables include moderators, mediators or short-term outcomes or even proximal measures of the ultimate outcome of interest

Other tailoring variables are genetics, family background, proteomics

Example: Adaptive Drug Court Program

- **Population:** drug abusing offenders assigned to drug court
- **Overall goal:** minimize recidivism and drug use
- **Critical treatment decisions:** which treatment to provide first?; which treatment to provide second?
- Marlowe et al. (2008, 2009, 2012)

Criminal Justice Review 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M.

Benasutti, Jason R. Croft and James R. McKay

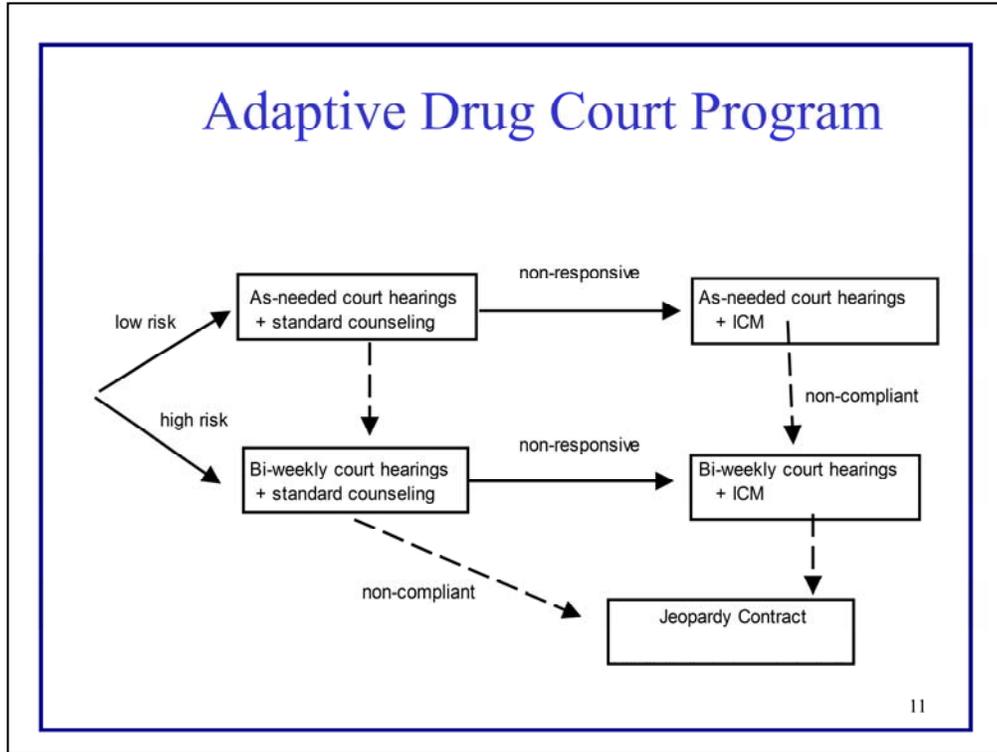
Adaptive Interventions in Drug Court: A Pilot Experiment

Adaptive interventions may optimize outcomes in drug courts: a pilot study. Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR. *Curr Psychiatry Rep.* 2009 Oct;11(5):370-6.

Adaptive Programming Improves Outcomes in Drug Court: An Experimental Trial by Douglas B. Marlowe, David S. Festinger, Karen L. Dugosh, Kathleen M. Benasutti, Gloria Fox, and Jason R. Croft *Criminal Justice and Behavior*, April 2012; vol. 39, 4: pp. 514-532.

minimize recidivism and drug use is operationalized by graduating from the drug court program

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee



All movement between steps or stages is operationalized!

High risk: ASPD or history of drug treatment otherwise low risk

These are assessed monthly:::

Noncompliance: is(1) falls to attend 2 or more counseling sessions or (2) fails to provide 2 or more scheduled urine specimens

Nonresponsive = (1) is attending sessions and completing program requirements, **and** (2) is not committing new infractions, **but** (3) provides 2 or more drug-positive urine specimens.

(from Marlowe paper:) A jeopardy contract involves “zero tolerance” for further violations of the rules of the program. Any further violation leads to a termination hearing, at which the participant is terminated from the program and sentenced on the original charge or charges unless he or she can provide a good-cause reason to be given another chance. The decision whether or not to permit another chance is within the discretion of the judge and is generally granted in approximately 30% of cases

Adaptive Drug Court Program Tailoring Variables

- Stage 1 Tailoring Variables: ASPD, Prior formal drug abuse treatment
- Stage 2 Tailoring Variables: Attendance at counseling sessions, Infractions, Providing scheduled urine screens, Positive urine specimens

Adaptive Drug Court Program Decision Rules

- Stage 1 Decision Rule: Provide group-based drug abuse counseling to all. **If** ASPD or Prior formal drug abuse treatment **then** provide bi-weekly court hearings. **Else** provide as-needed court hearings.
- Stage 2 Decision Rule: **If** committed an infraction or missed 2 or more counseling sessions or missed 2 or more urine screens **then** step up court supervision. **Else if** 2 or more positive urine specimens **then** step up treatment to ICM. **Else** continue on stage 1.

ICM is intensive case management, includes individual counseling as well as help with other aspects of life (housing, etc.)

Other Examples of Adaptive Health Interventions

- Brooner et al. (2002, 2007) Treatment of Opioid Addiction
- McKay (2009) Treatment of Substance Use Disorders
- HIV-Causal Collaboration (2011) Treatment of HIV
- Rush et al. (2003) Treatment of Depression

Brooner uses a two component adaptive txt strategy, one component has to do with txt and the other with encouragement to adhere.

One steps up/down intensity and type of counseling sessions based on negative urines and adherence

One steps up/down behavioral contingencies based on adherence to counseling sessions.

Rules are explicit.

McKay has a book on this topic– see **Treating Substance Use Disorders With Adaptive Continuing Care (Hardcover)** by [James R. McKay](#)

When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study.

[HIV-CAUSAL Collaboration](#), [Cain LE](#), [Logan R](#), [Robins JM](#), [Sterne JA](#), [Sabin C](#), [Bansi L](#), [Justice A](#), [Goulet J](#), [van Sighem A](#), [de Wolf F](#), [Bucher HC](#), [von Wyl V](#), [Esteve A](#), [Casabona J](#), [del Amo J](#), [Moreno S](#), [Seng R](#), [Meyer L](#), [Perez-Hoyos S](#), [Muga R](#), [Lodi S](#), [Lanoy E](#), [Costagliola D](#), [Hernan MA](#).

[Ann Intern Med](#). 2011 Apr 19;154(8):509-15.

The decision rules used by Brooner et al and McKay are quite detailed, and based on explicit actions by patient, whereas in contrast the Rush et al study (Texas Medication Algorithm Project) appears to be more loosely structured; the clinician uses clinical judgment to decide if depression levels are clinically significant and thus an augmentation or switch in treatment intensity is needed. The particular secondary treatment is chosen out of a set of specified alternatives and depends on clinical judgment/patient preference.

Outline

- What are Adaptive Health Interventions?
- Why use Adaptive Health Interventions?
- Adaptive Health Intervention Design Goals
- What does an Adaptive Health Intervention include?
- Summary & Discussion

Why Adaptive Health Interventions?

- 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

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This is really “why do we need to consider a sequence of treatments?”

Why Adaptive Health Interventions?

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

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Why Adaptive Health Interventions?

3) Treatment is burdensome

Treatment required over long time periods is burdensome

Non-adherence leads to relapse or loss of positive effect

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Why not combine all possible efficacious therapies and provide all of these to the 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!

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Why not give a universal intervention to all for a sufficiently long time??

These are all reasons why you should not provide MORE treatment than is needed.

Only provide MI to people who need motivation to adhere.

That is a multi-component fixed treatment is not practical or is too costly or would not result in good adherence

A principle of adaptive tx strategies is to provide no more than needed to accomplish desired result!

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Main Adaptive Health Intervention Design Goal is to Improve Outcomes

- Maximize the strength of the Adaptive Health Intervention
 - by well chosen tailoring variables, well measured tailoring variables, well conceived decision rules & well implemented decision rules

CLARIFICATION NOTE: Here we are discussing the design of the Adaptive Health Intervention (hence “treatment design”). We are not discussing the design of a trial to inform the development of an AHI—that’s the next module on “trial design”.

Use behavioral/social/biological theory, clinical experience, expert opinion, consultation with clinical staff, review of extant literature to help select the tailoring variables and form the decision rules.

Another Important Adaptive Health Intervention Design Goal is to...

- Maximize replicability in future real-world implementation conditions and experiments (or research studies)
 - by clearly defining the treatment strategy & by fidelity of implementation

To achieve this goal, AHI should be explicit. We have the most confidence in an Adaptive Health Intervention when its effects are replicable with different experimenters, different clinical staff, different locations, etc

Recall the definition of an AHI

- **Adaptive Health Interventions** 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).

Tailoring is achieved by use of a decision rules. Takes ongoing info (past response, adherence, burden, etc) and outputs txt level type

Considerations re Critical Decisions

- Which treatment decisions are critical and need to be guided (e.g. manualized, structured) ?
 - Which decisions are likely influenced by non-systematic variance?
 - Which decisions are likely influenced by systematic bias?

variance: different staff would provide the same individual with different treatments

Non-systematic variance: this variance is due to issues unrelated to the individual (staff member is in a hurry, staff member is tired, last patient of the day, etc.)

Systematic variance: this variance is due to (unconscious) bias on the part of the staff member. One staff member connects to the individual whereas the other staff member does not. Racial or gender or age bias lead to different treatment recommendations.

Adaptive Health Intervention 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

In order to understand how to achieve our design goals it is important to understand what constitutes the treatment.

Aspects of the site such as individual staff, schools, treatment sites, etc. are often not part of the intervention. Rather, they are often sources of extraneous variance

Measurement is particularly an issue if you have a theory based adaptive txt strategy.

This bundle (tailoring variable→ decision rule→ implementation) denotes one txt. Condition

Considerations re 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.

Actually it is the optimal txt that varies by individual characteristics.
To help understand this consider the following example.

Adaptive Aftercare for Alcohol Dependent Individuals

- Hypothetical Study (do this study in your head): Alcohol dependent individuals on NTX; after 8 weeks randomize individuals to continue on NTX or to an augment of NTX with CBI
- Result of hypothetical study: Among individuals who had returned to heavy drinking, NTX+CBI performs better than NTX only. However there is little or no difference for individuals who were maintaining a more sober lifestyle.

Adaptive Aftercare for Alcohol Dependent Individuals

- Individuals who return to heavy drinking while on Naltrexone (NTX) need additional help to maintain a non-drinking lifestyle.
- Tailoring variable is heavy drinking
- Providing CBI to non-heavy drinkers is costly (and no better than continuing NTX alone).
- Implication: Provide NTX +CBI to individuals who are drinking heavily. NTX only is sufficient for individuals who are maintaining a non-heavy drinking lifestyle.

tailoring variable: proximal measure of heavy drinking –a proximal value of primary outcome!

This is one of those cases where a cost might be incorporated into the response, Y.

Technical Interlude!

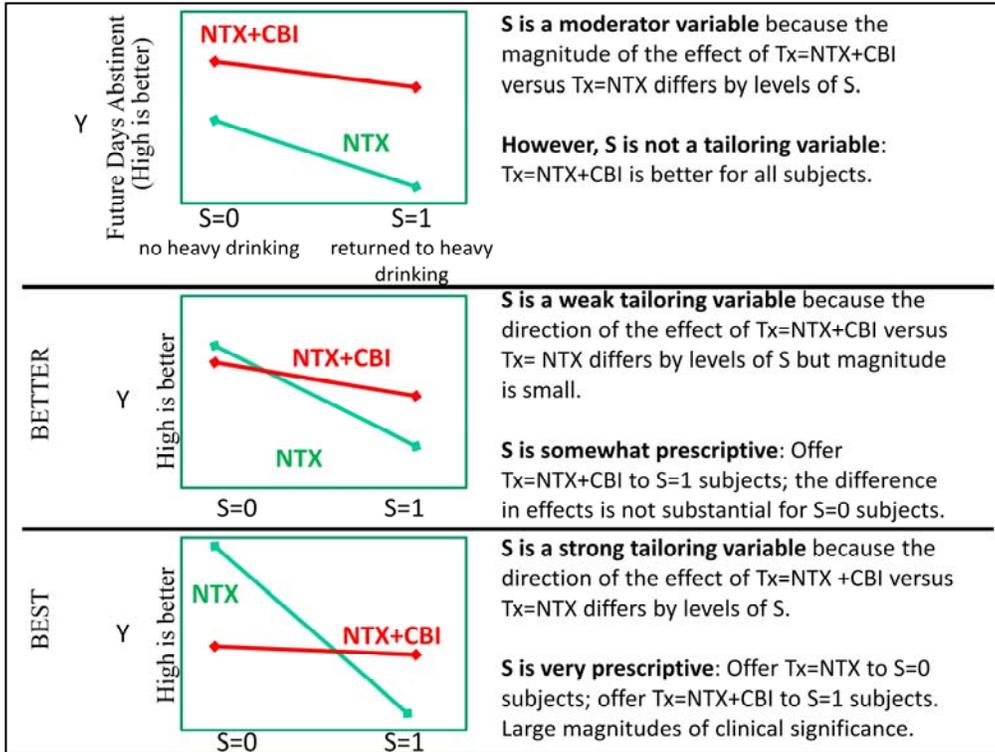
S =tailoring variable (heavy drinking)

Tx =treatment type (NTX vs NTX+CBI)

Y =primary outcome (days abstinent, high is preferred)

$$Y = \beta_0 + \beta_1 S + \beta_2 Tx + \beta_3 S Tx + error$$
$$= \beta_0 + \beta_1 S + (\beta_2 + \beta_3 S) Tx + error$$

If $(\beta_2 + \beta_3 S)$ is zero or negative for some S and positive for others then S is a tailoring variable.



Tailoring variables

- Tailoring variables are moderators but they may also be
 - Baseline variables
 - Mediators
 - Short-term outcomes
 - Proximal measures of the ultimate outcome of interest.
 - Time-varying versions of all of the above

They can certainly be biological (proteomics, genetics, blood sample data, saliva data, etc....), including repeated measurements of biological data.

Measurement of Tailoring Variables

- Reliability -- high signal to noise ratio
- Validity -- unbiased

Unreliability means that you are making unsystematic assignment of dose – getting close to random assignment.

Invalid measure will weaken intervention effect (assuming your theory is correct) as you will be systematically assigning the wrong dose.

Alcohol aftercare study included weekly self report, but biological is not weekly – oh no!.

Self-report: Time-Line Follow-Back (TLFB).

Biological: Carbohydrate Deficient Transferrin (CDT).

Timing of Tailoring Variable Collection

- Tailoring variable should be assessed at sufficiently frequent intervals so that (non) response is detected in a timely manner.
- Too infrequent and an individual's condition may deteriorate so much that readily available rescue options are ineffective.
- Too frequent assessment may result in dependence or non-adherence

How frequently to measure a tailoring variable may be a critical decision!!

That is, this may be part of the AHI in the sense that for some individuals, you might assess (non) response more/less frequently than for other individuals.

Adaptive Aftercare for Alcohol Dependent Individuals

- Example:** The tailoring variable is heavy drinking days. Should we measure this variable weekly or twice a week?

Derivation of Decision Rules

- Articulate a theoretical model for how treatment effect on key outcomes should differ across values of the tailoring variable.
- 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?”

In order to achieve a particular desired treatment effect different amounts or types of treatment may be needed by different individuals

In alcohol aftercare study they know from prior studies that people who relapse to heavy drinking while on naltexone within first two months rarely recover.

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.

Use staff to help brainstorm about operationalizing the rules.

Operationalize the Decision Rules

- Bad:** Individuals who are drinking excessively are switched to NTX+MM+CBI
- Better:** Individuals who experience 3 or more heavy drinking days are non-responders and are switched to NTX+MM+CBI.
- Best:** As soon as 3 or more heavy drinking days occur within weeks 3-8 while on NTX+MM, the person is declared a non-responder and switched to NTX+MM+CBI. Otherwise, remain on NTX+MM.

Adaptive Aftercare for Alcohol Dependent Individuals

- **Example:** Suppose an individual misses his weekly clinic visit. Then the number of heavy drinking days in the prior week is missing.
- Should we wait until the following week to decide if the individual is a non-responder or should we call the individual a non-responder immediately?
 - This is a clinical (treatment design) issue.

Summary & Discussion

- Adaptive Health Interventions are attractive alternatives to fixed treatments
 - if in a comparable fixed treatment, significant variation in treatment effect would be expected as a function of identifiable tailoring variables, across participants and/or within participants over time

Summary & Discussion

Adaptive Health Interventions enhance the potency of the treatment if

- by increasing salience and negative effects, they improve adherence
- by reducing waste it becomes possible to devote additional resources to higher-risk individuals who can benefit from them.

Summary & Discussion

- 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
 - on when/how to allow clinical judgment.

Questions?

More information

L.M Collins, S.A. Murphy and K.A. Bierman (2004), A Conceptual Framework for Adaptive Preventive Interventions, *Prevention Science* 5:185-196.

S.A. Murphy & J.R. McKay (2004), Adaptive Treatment Strategies: an Emerging Approach for Improving Treatment Effectiveness. *Clinical Science* (Newsletter of the American Psychological Association Division 12, section III: The Society for the Science of Clinical Psychology) Winter 2003/Spring 2004

L.M. Collins, S.A. Murphy, V. Nair & V. Strecher (2005), A Strategy for Optimizing and Evaluating Behavioral Interventions, *Annals of Behavioral Medicine*. 30:65-73.

S.A. Murphy, L.M. Collins, A.J. Rush (2007). Customizing Treatment to the Patient: Adaptive Treatment Strategies. *Drug and Alcohol Dependence*.. 88(2):S1-S72.

Discussion & Practice Exercise

Exercise: *Write/draw one simple AHI to address a disorder in your field. How to do this: a) Identify two sequenced critical decision points. b) Identify a tailoring variable for each decision point. c) Identify a treatment option for each value/level of the tailoring variable.*

Discussion Question: *How are AHIs similar/different to the types of behavioral interventions we typically think about?*

Extra Slides

Another Important Adaptive Health Intervention Design Goal is to...

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

To achieve this goal, AHI should be explicit. We have the most confidence in an Adaptive Health Intervention when its effects are replicable with different experimenters, different clinical staff, different locations, etc

Implementation of the AHI in a Trial

- Try to implement decision rules universally, applying them consistently across subjects, time, site & staff members.
- We want to avoid treating some subjects differently from others due to factors that are not in the decision rules.
 - The non-systematic component introduces random error and increases variance.
 - The systematic component harms replicability by increasing the plausibility of alternative explanations for the (in)effectiveness of the Adaptive Health Intervention.

If rules are not implemented universally, some persons are treated differently from others, because the dosage assignment is based in part on factors that do not figure in the decision rules and may be unique to a certain individual, time, or situation.

Implementation of the AHI in a Trial

- Try to implement rules universally, applying them consistently across subjects, time, site & staff members.
- Staff may be resistant to implementing the rules universally because
 - Missing but needed tailoring variables
 - Measured tailoring variable lacks validity
 - The way the tailoring variable weighs different criteria may be questioned.
 - Decision rules are ambiguous
 - Insufficient training

Staff perceive dosage rules are inappropriate in a particular case
To the extent that individuals with the same tailoring variable values are assigned dosages by relying on ad hoc procedures rather than the established dosage assignment rules, there will be problems with replicability.

The rule is like the manual in a manualized therapy.

Implementation of the AHI in a Trial

- 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.
- Document the value of the tailoring variable.

If it is a big deal to make an exception then staff must come up with a cogent argument that you can use to help plan future implementations.

This helps you

- 1) Future revision of rule
- 2) Indicates if there is a need for further staff training
- 3) May indicate that you need to be clearer in articulating the purpose of a txt component.

Role of Clinical Judgment in Derivation of the Decision Rules

How should the decision rules include clinical judgment? How should clinical judgment be structured?

- Via structured measurements that enter into tailoring variable?
- Via a choice among a restricted set of options?

Clinical judgment is used to inform the development of the decision rules and to produce structured measurements of tailoring variable

Should clinical judgment be used to select among a limited set of dosages (Although using clinical judgment to inform dosage decisions in this way may seem useful from a clinical standpoint, it is important to consider that this procedure renders clinical judgment a part of the decision rules, and therefore a part of the overall treatment.)

Is the following desirable?: Decision rules may include the less structured clinical judgment, e.g. Clinician selects one treatment in a set of recommended treatments for non-responders who are non-adhering
Clinician can declare non-response only after 6 weeks (with guidelines for what constitutes non-response)

In clinical judgment—how can local knowledge be used in a replicable way? Should local knowledge be used to choose between equivalent txt's?.

Sequential, Multiple Assignment, Randomized Trials

Module 2

Getting SMART About Developing Individualized,
Adaptive Health Interventions

6th Annual Advanced Training Institute on Health
Behavior Theory, Madison, Wisconsin, July 19

Daniel Almirall & Susan A. Murphy



45 minutes

Sequential Multiple Assignment Randomized Trials (SMARTs)?

What are SMARTs?

Why do we need SMARTs?

Discuss the role of critical decisions and treatment options to plan and provide the rationale for a SMART

Utilizing theory to plan a SMART

Compare SMARTs to using a multiple-RCT approach

Discuss SMART design principles

What are typical primary and secondary aims in a SMART?

Sample size considerations

De-bunk misconception that SMARTs necessarily require large sample sizes.

Before We Begin...Throughout This
Module, Keep in Mind the End-of-
Module Practice Exercise and Discussion
Question

Exercise: *Begin thinking about a SMART design
in your research.*

Discussion Question: *What is the primary
purpose of a SMART? How are SMARTs
different from standard RCTs?*

Some Critical Questions in Adaptive Health Intervention 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 (experimental) 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
- Summary & Discussion

What is a SMART Study?

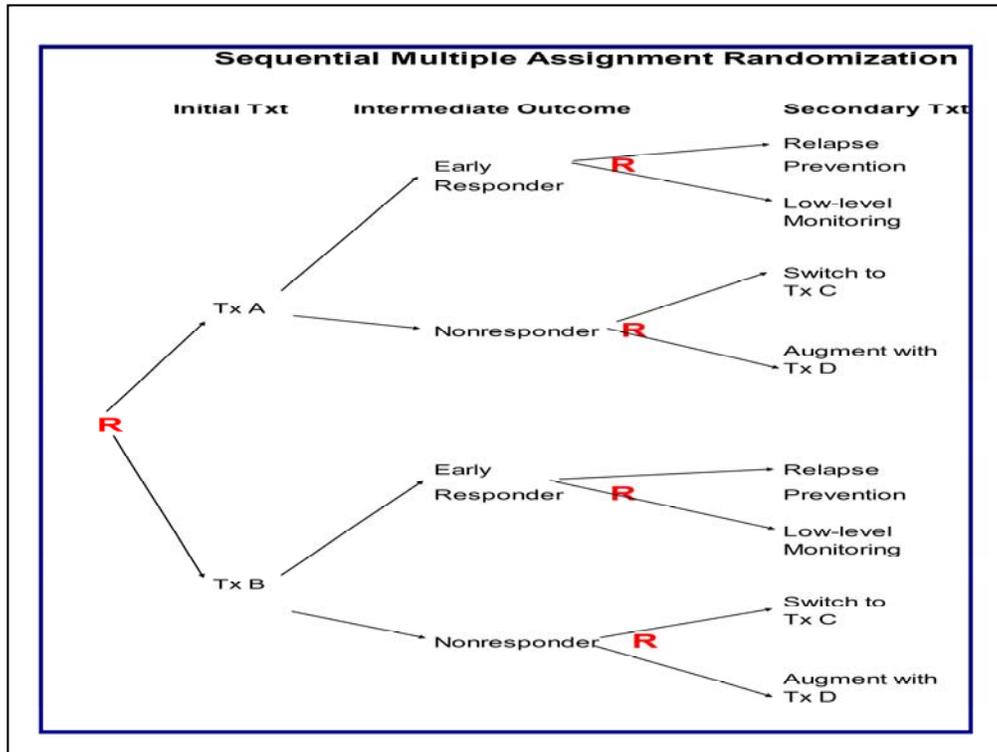
What is a sequential multiple assignment randomized trial (SMART)?

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

Goal is to inform the construction of adaptive health interventions.

In statistics people may call these multistage trials (the randomization at each stage is assumed)

The randomizations at each stage allow us to learn what the best treatment is for that stage.



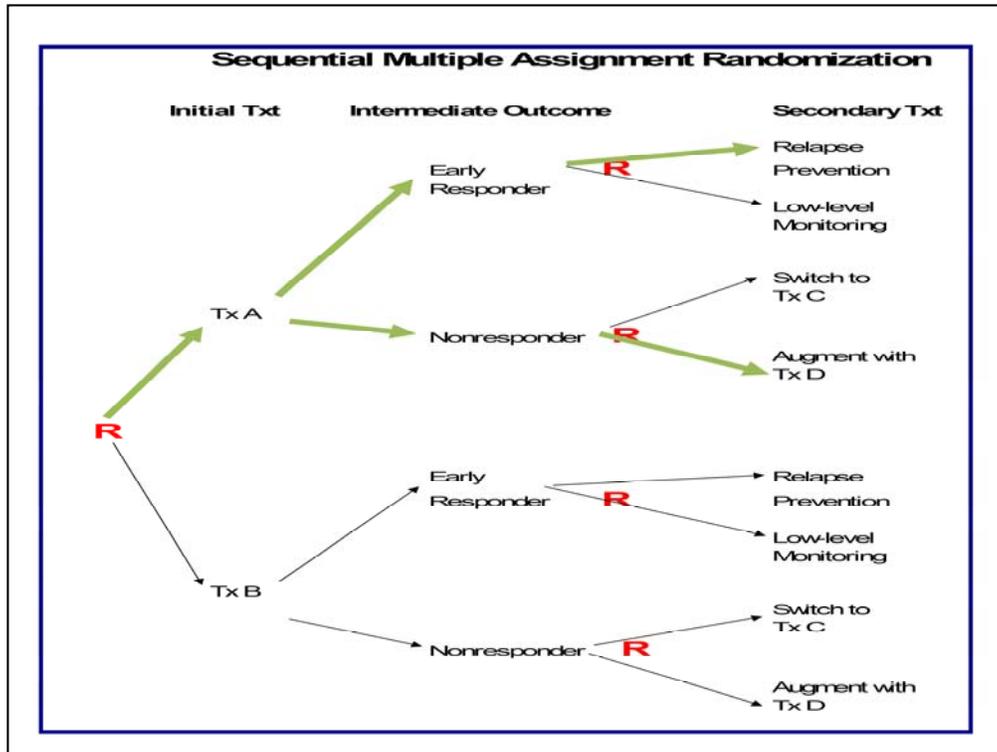
Hypothetical trial: Outcome is not shown but is on far right. The randomizations can take place up front.

Equal randomization

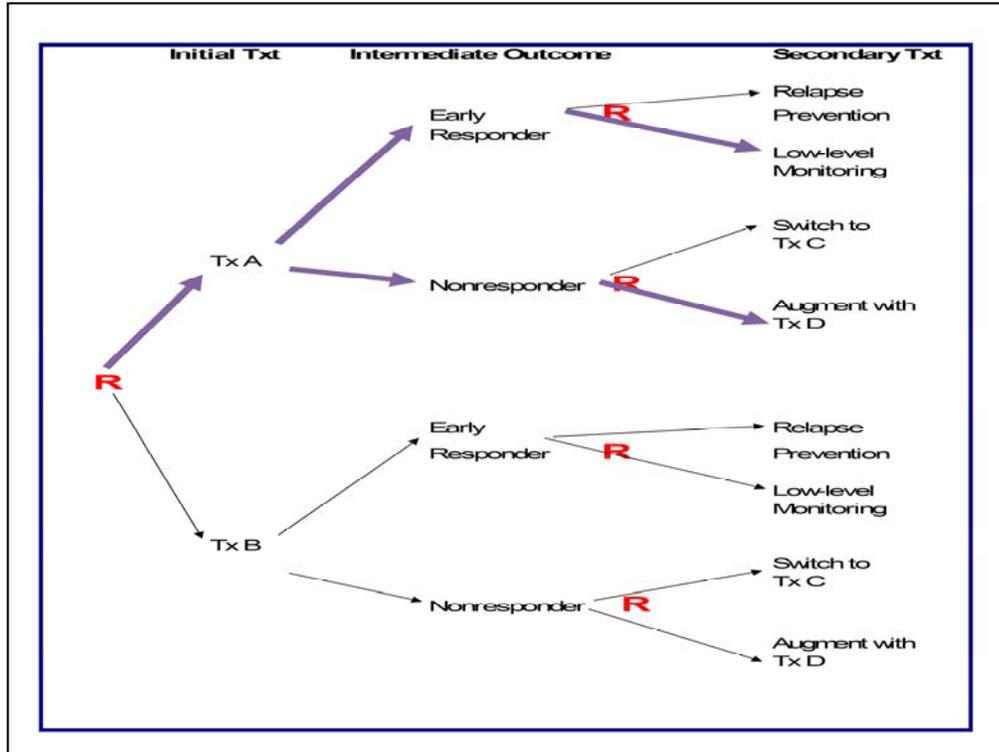
Usual reaction is (1) I'm worried about sample size and

(2) This looks awfully complicated.

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



An embedded adaptive health intervention



Another embedded adaptive health intervention!

Outline

- What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
- Why SMART experimental designs?
- Trial Design Principles
- Summary & Discussion

Challenges in constructing Adaptive Health Interventions

- Delayed, Prescriptive & Sample Selection Effects

---sequential multiple assignment randomized trials (SMART)

- Adaptive Health Interventions are Multi-component Treatments

---series of screening/refining randomized trials prior to confirmatory trial (MOST).

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L.M. Collins, S.A. Murphy, V. Strecher (2007). The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent e-Health Interventions. *American Journal of Preventive Medicine* , 32(5S):S112-118

Alternate Approach I to Constructing an Adaptive Health Intervention

- Why not use data from multiple trials to construct the adaptive health intervention?
- 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 second, separate randomized trial of secondary treatments.

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 health intervention

Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive health intervention?

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.

counseling and then if respond, monitoring with low level telephone counseling.

Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive health intervention?

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.

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 responsiveness to future treatment; see Thall et al. (2007) for an example of the latter in cancer research.

A Consequence of Delayed Therapeutic Effects

- Comparisons of initial treatments based on a acute 3 month outcome may result in a different result from a comparison of these two initial treatments based on a 6 month outcome.
- Restricting to 6 month outcomes, a comparison of initial treatments followed by usual care in months 4-6 may differ from a comparison of initial treatments followed by one of several maintenance therapies in months 4-6.

Harnessing Delayed Therapeutic Effects

- Our goal is to ensure that the subsequent treatment builds on gains achieved by prior treatments even when the participant initially appears non-responsive.
- We want large positive delayed effects (i.e. large positive cross-over effects are great!)
- We want to prevent negative delayed effects.

Harnessing Delayed Therapeutic Effects

Using data from multiple trials to construct the adaptive health intervention is less helpful in harnessing delayed therapeutic effects because we need to assess the combined effect of a sequence of treatments.

Prescriptive Effects

Why not use data from multiple trials to construct the adaptive health intervention?

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 enhanced adherence support during the maintenance or aftercare phase.

Sample Selection Effects

Why not use data from multiple trials to construct the adaptive health intervention?

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.

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.

An Different Example of Sample Selection Effects

A scientist who has conducted non-responder trials comparing treatment A versus B decides to conduct a SMART. The scientist reports that when conducting the SMART he discovers that a large fraction of the non-responders do not want to be randomized to either treatment A or B.

What has happened?

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 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 initially in an adaptive txt strategy

Alternate Approach II to Constructing an Adaptive Health Intervention

- Theory, clinical experience and expert opinion are critical in the development of adaptive health interventions
- However, why not use theory, clinical experience and expert opinion to *completely* construct the adaptive health intervention and then compare this strategy against an appropriate alternative in a confirmatory randomized two group trial?

Why constructing an adaptive health intervention and then comparing the strategy against a standard alternative is not always the answer.

- Don't know why your adaptive health intervention worked or did not work. Did not open black box.
- We don't know what components of the adaptive health intervention are (in)active. Is the first stage treatment or the second treatment or the tactical decisions regarding the criterion for nonresponse or the timing of assessment of nonresponse sequence effective?

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Meeting the Challenges

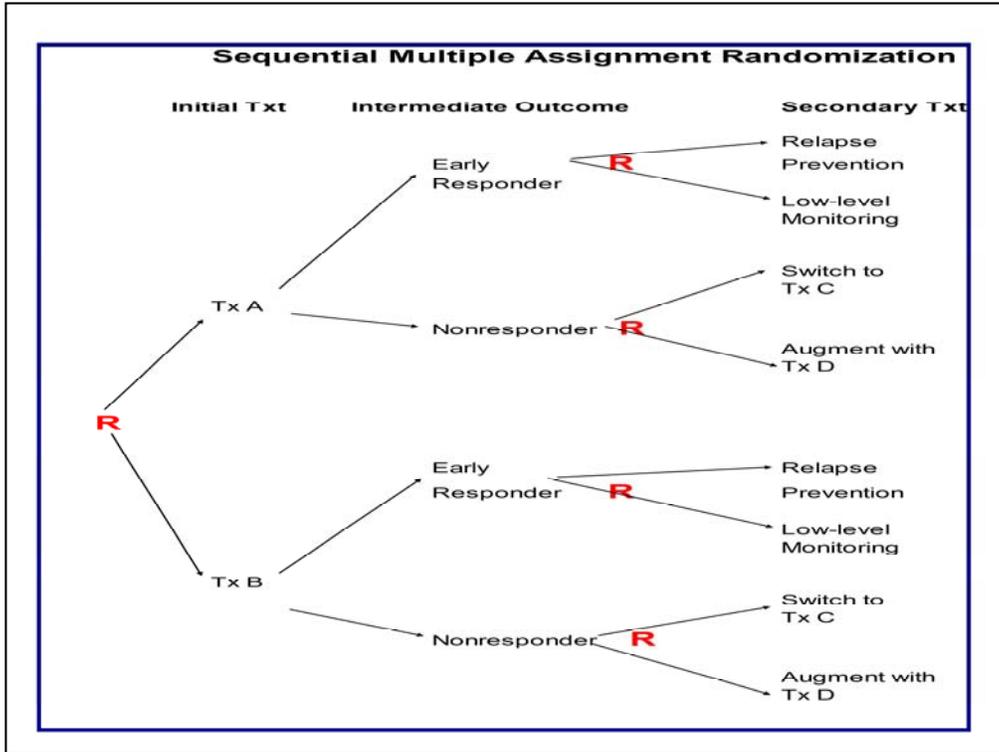
Delayed/Prescriptive/Sample Selection Effects:
SMART

Developing Multi-Component Interventions:
Screening/refining randomized trials prior to a
confirmatory trial (MOST).

The SMART design is one of the
screening/refining randomized trials in MOST ²³

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

MOST multistage optimization strategy



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

After lunch we will discuss some of these designs in some detail!

Outline

- What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
- Why SMART experimental designs?
- Trial Design Principles
- Summary & Discussion

Critical Decisions

- Choose two or three critical decisions to address.
- Examples of critical decisions
 - Sequencing decisions: Which treatment to try first? Which treatment to try if individual shows signs of nonresponse? Which treatment to try if the individual is doing well?
 - Timing decisions: How soon do we declare nonresponse? How soon do we declare response?
- Which decisions are most controversial or need investigation? Which decisions are likely to have the biggest impact on the outcome?

In the use of naltrexone for alcohol dependence different researchers and clinicians use different criteria for non-response ranging from at least 5 heavy drinking days to at least 2 heavy drinking days. Yet 8 weeks of little to no heavy drinking is a common criterion for response.

So one of the critical decisions to investigate was the heavy drinking days trigger for nonresponse. We decided that it was less important to investigate the best duration of little to no heavy drinking before declaring response.

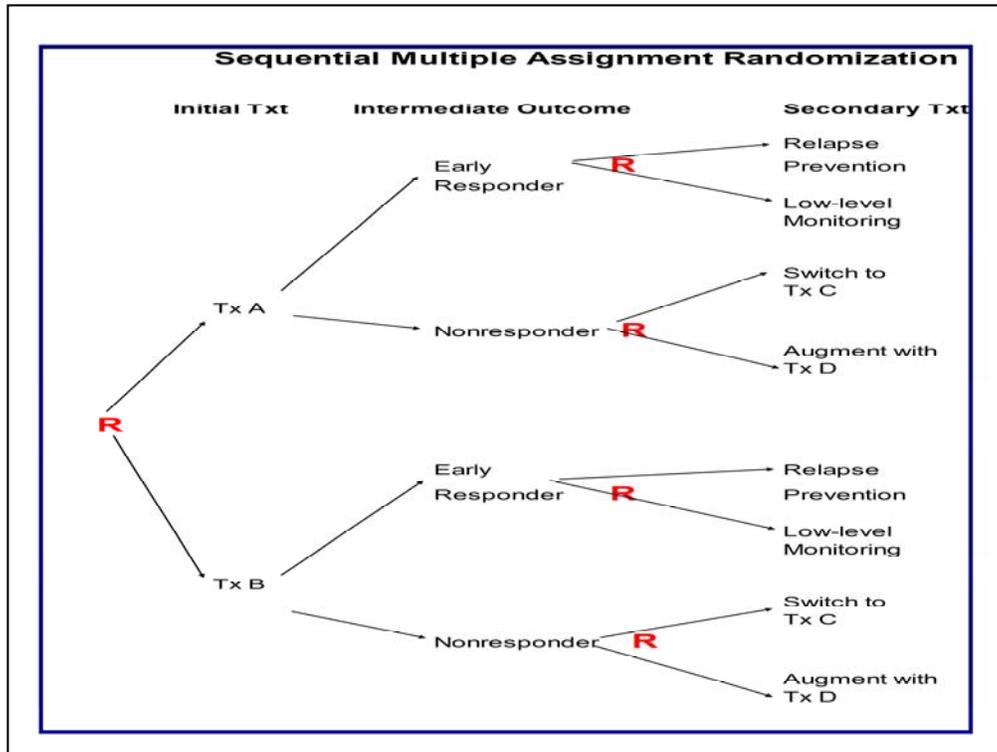
Critical Decisions

- In planning the study of Naltrexone for alcohol dependence, we realized that different researchers and clinicians use different criteria for non-response ranging from at least 5 heavy drinking days to at least 2 heavy drinking days.
 - This timing decision became one of the critical decisions to investigate.
- Other critical decisions involved which maintenance treatment to provide responders and which treatment to provide nonresponders.

See H. Lei, I. Nahum-Shani, K. Lynch, D. Oslin and [S.A. Murphy A SMART Design for Building Individualized Treatment Sequences](#), *The Annual Review of Clinical Psychology* (2012), *Review in Advance* first posted online on December 12, 2011 for greater detail.

SMART Treatment Stages

- Each treatment stage (i.e., phase) in the SMART corresponds to a critical decision.
- We randomize participants at each treatment stage among different treatment options.
- The first stage of the alcohol dependence study involved randomization to either a “ ≥ 5 HDD nonresponse definition” or a “ ≥ 2 HDD nonresponse definition.”



What are the critical decisions in this hypothetical trial? What are the stages?

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 health intervention.

Note we considered different txt's for the responders as compared to the nonresponders. A SMART does not need to restrict the class of treatments by responder status.

Collect information on adherence, symptoms, side effects, problems with co-occurring disorders, etc.

SMART Design Principles

- Choose primary hypotheses that are both scientifically important and aid in developing the adaptive health intervention.
 - Power trial to address these hypotheses.
- Choose secondary hypotheses that further develop the adaptive health intervention and use the randomization to eliminate confounding.
 - Trial is not necessarily powered to address these hypotheses.

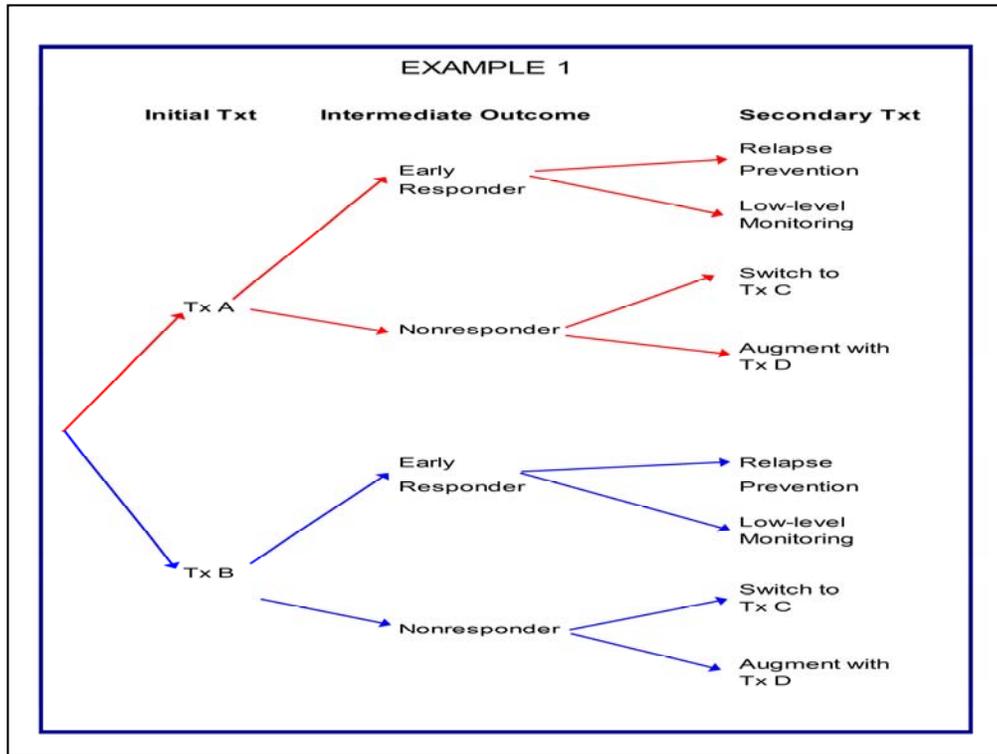
SMART Designing Principles: Primary Hypothesis

- 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

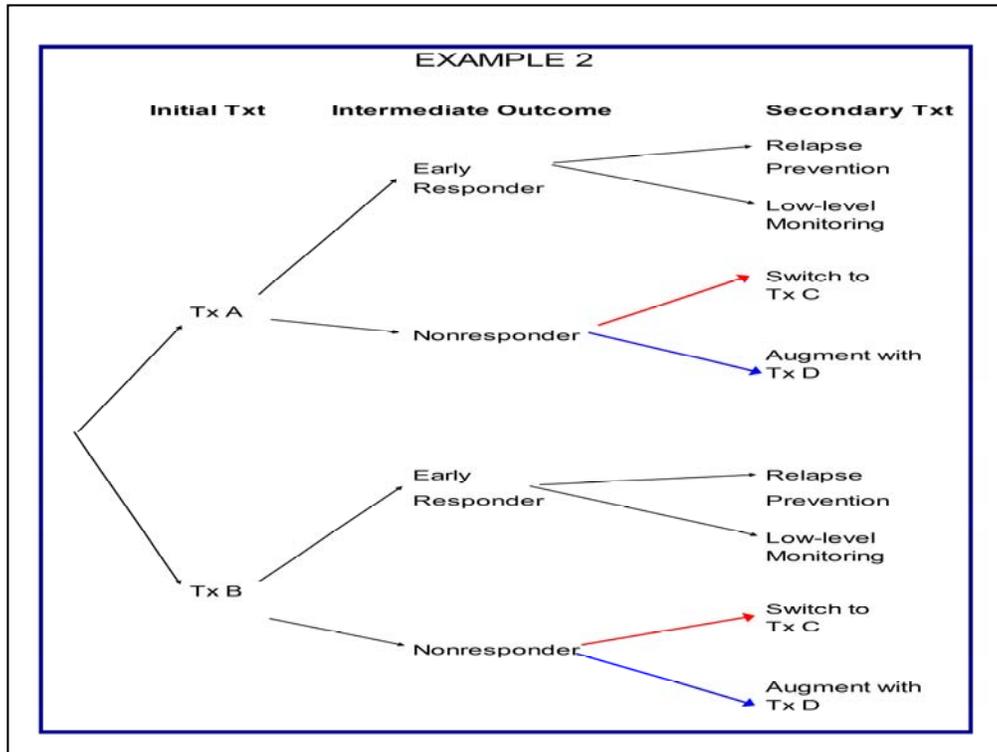
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

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.

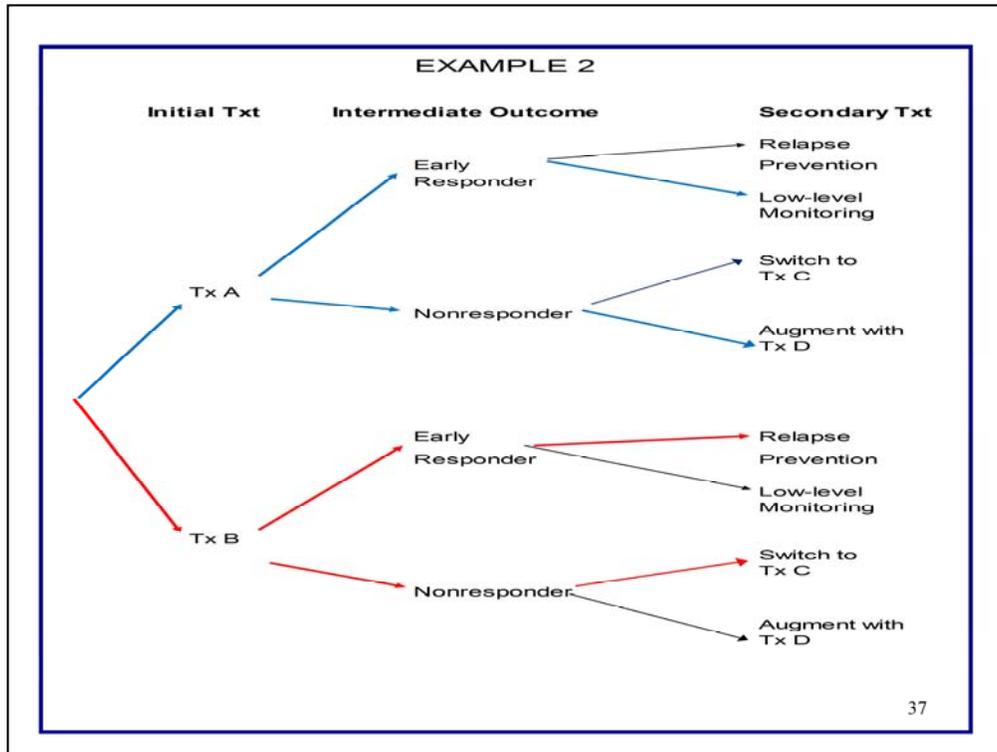


A study of nonresponders in which one controls the tx's to which people don't respond to.

SMART Designing Principles: Primary Hypothesis

- EXAMPLE 3: (*sample size is less constrained*):
Hypothesize that embedded adaptive health intervention 1 (in blue) results in improved symptoms as compared to embedded adaptive health intervention 2 (in red)

These are main effects a la' ANOVA



Sample size formula for this SMART to compare the red versus blue embedded adaptive health interventions is given in [S.A. Murphy \(2005\), *An Experimental Design for the Development of Adaptive Treatment Strategies*, *Statistics in Medicine*. 24:1455-1481](#)

Requires a weighted analysis Murphy et al (2001)

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

Example Sample Sizes		
N=trial size		
	Example 1	Example 2
$\Delta\mu/\sigma = .3$	N = 402	N = 402/initial nonresponse rate
$\Delta\mu/\sigma = .5$	N = 146	N = 146/initial nonresponse rate
$\alpha = .05,$ power = $1 - \beta = .85$		

Sigma for example 1 is the std of primary outcome of patients initially assigned tx A (or B)

recommendation: use the Sigma with the highest variance.

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

recommendation: use the Sigma with the highest variance.

Throughout working assumptions are equal variances and normality

Sample sizes calculated on the website:

http://hedwig.mgh.harvard.edu/sample_size/quant_measur/para_quant.html

In the case of example 3, multiply N by 2. Sigma for example 3 is the std of the primary outcome of patients assigned the blue adaptive health intervention (or red adaptive health intervention).

An analysis that is less useful in the development of adaptive health interventions:

Decide whether treatment A is better than treatment B by comparing proportion of early responders.

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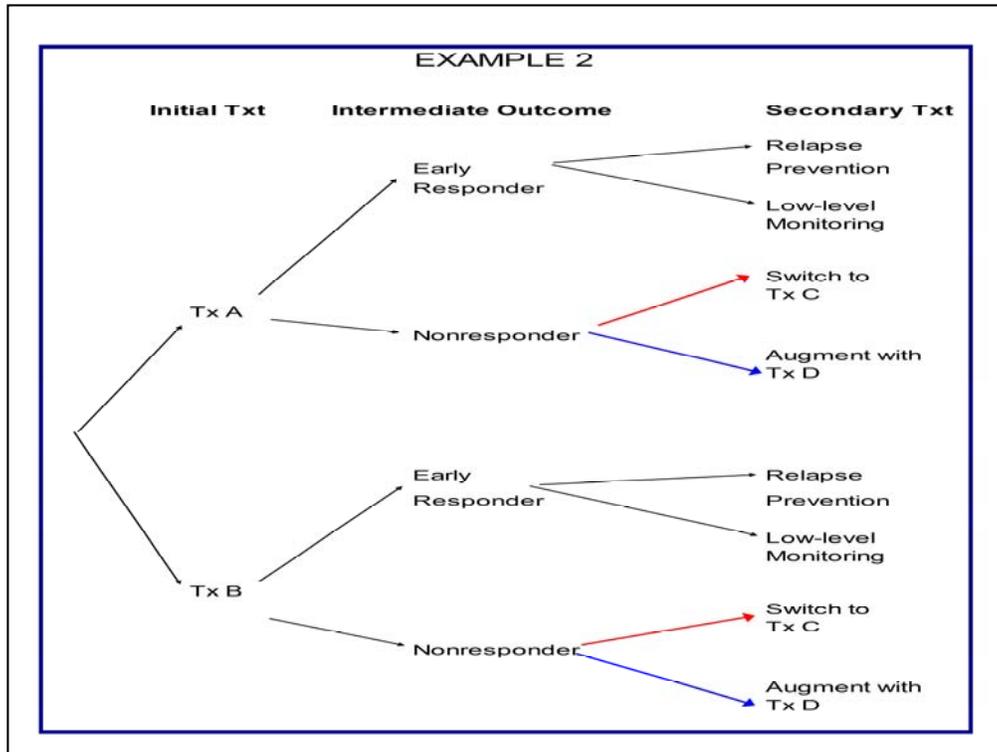
It is interesting (& certainly helps tell the story of which adaptive health intervention is best) but this is not a useful aim in the development of adaptive health interventions. Therefore, while we will analyze this using the SMART study data, we will not power the study based on this question.

SMART Designing Principles

- Choose secondary hypotheses that further develop the adaptive health intervention 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.

Summary & Discussion

- We have a sample size formula that specifies the sample size necessary to detect an embedded adaptive health intervention that results in a mean outcome δ standard deviations better than the other embedded adaptive health interventions 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>

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Practice Exercise and Discussion Question

Exercise: *Begin thinking about a SMART design in your research. What would the first randomization be? The second randomization? How can you incorporate the AHI you developed in Module 1 into this design?*

Discussion Question: *What is the primary purpose of a SMART? How are SMARTs different from standard RCTs?*

Questions?

More information

S.A. Murphy, K.G. Lynch, J.R. McKay, D. Oslin, T. TenHave (2007). Developing Adaptive Treatment Strategies in Substance Abuse Research. *Drug and Alcohol Dependence*, 88(2):S24-S30

L.M. Collins, S.A. Murphy, V. Strecher (2007). The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent e-Health Interventions. *American Journal of Preventive Medicine*, 32(5S):S112-118

A.I. Oetting, J.A. Levy, R.D. Weiss, S.A. Murphy (2011), Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies,, *Causality and Psychopathology: Finding the Determinants of Disorders and their Cures*, (P.E. Shrout, K.M. Keyes, K. Ornstein, Eds.) Arlington VA: American Psychiatric Publishing, Inc, pgs. 179-205

I. Nahum-Shani, M. Qian, D. Almira, W. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2012). Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. *To appear in Psychological Methods*

Very technical:

S.A. Murphy and D. Bingham (2009). Screening Experiments for Developing Dynamic Treatment Regimes. *JASA*. 184:391-408.

Learn More About AHIs and SMART Designs

- Susan A. Murphy and I have developed a 2-day workshop on Adaptive Health Interventions and SMART Designs. The workshop goes into quite a bit more detail than we were able to cover today in just 2.5 hours. The 2-day course includes data analysis strategies with SAS code and simulated data sets mimicking real-world SMART trials.
- Get the slides/files for the 2-day workshop:
<http://www-personal.umich.edu/~dalmiral/atsworkshops.html>