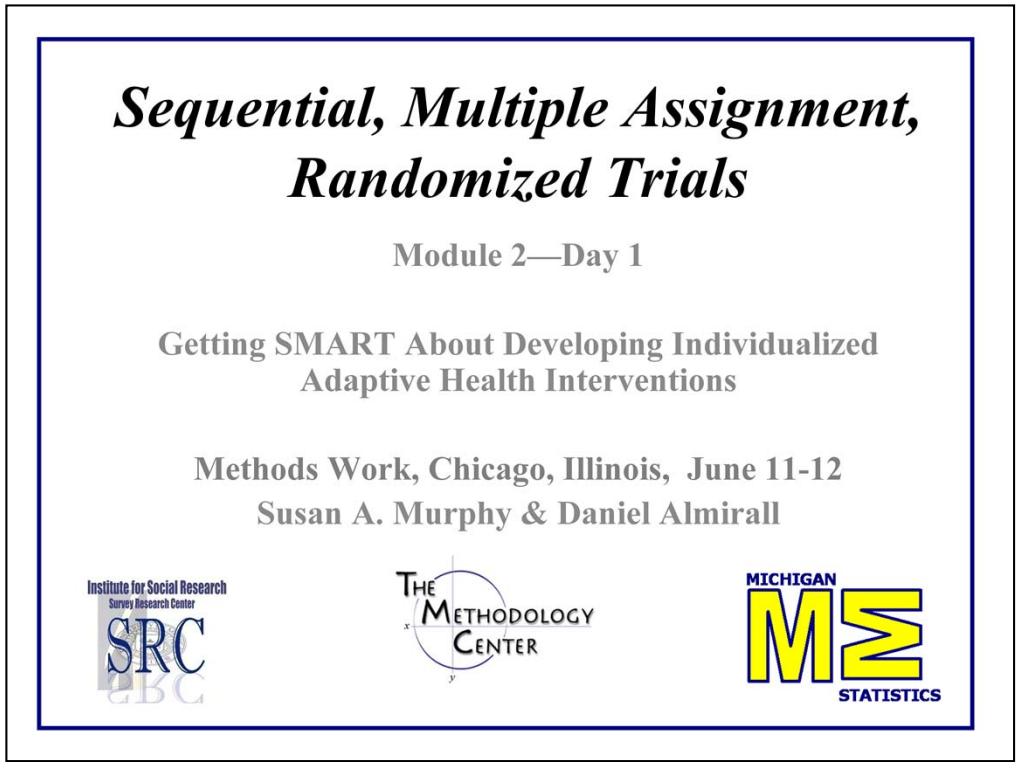


60 minutes

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 rational 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.

Some Critical 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
- Summary & Discussion

What is a SMART Study?

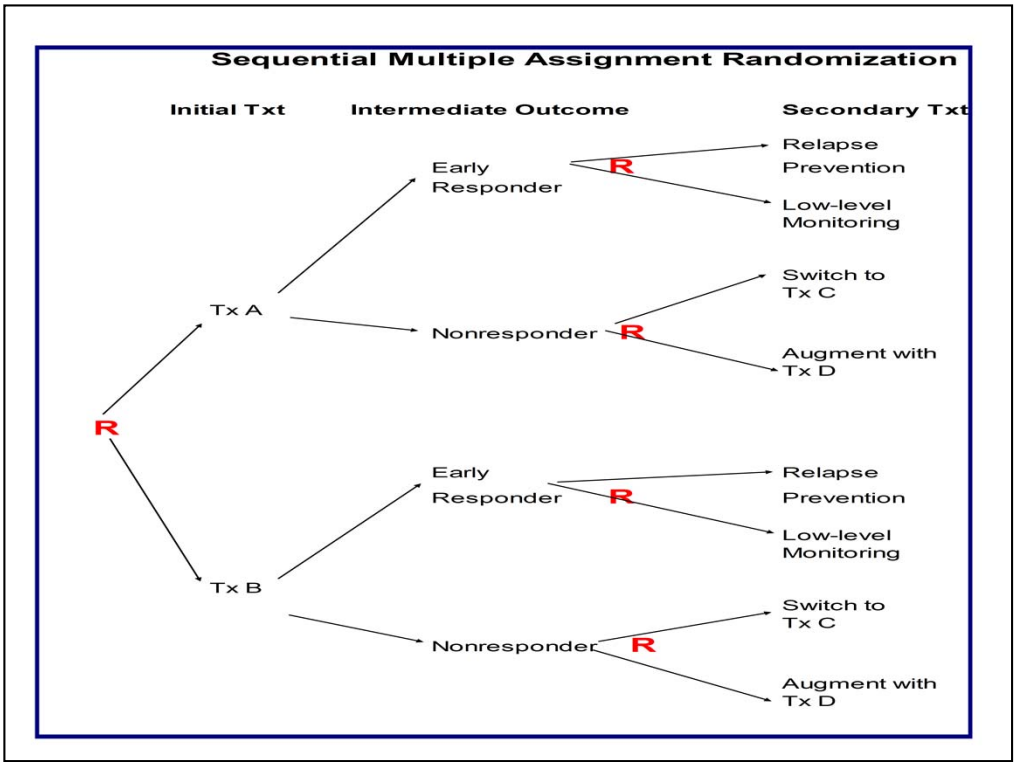
What is a sequential multiple assignment randomized trial (SMART)?

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 treatment strategies.

In stat. 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.



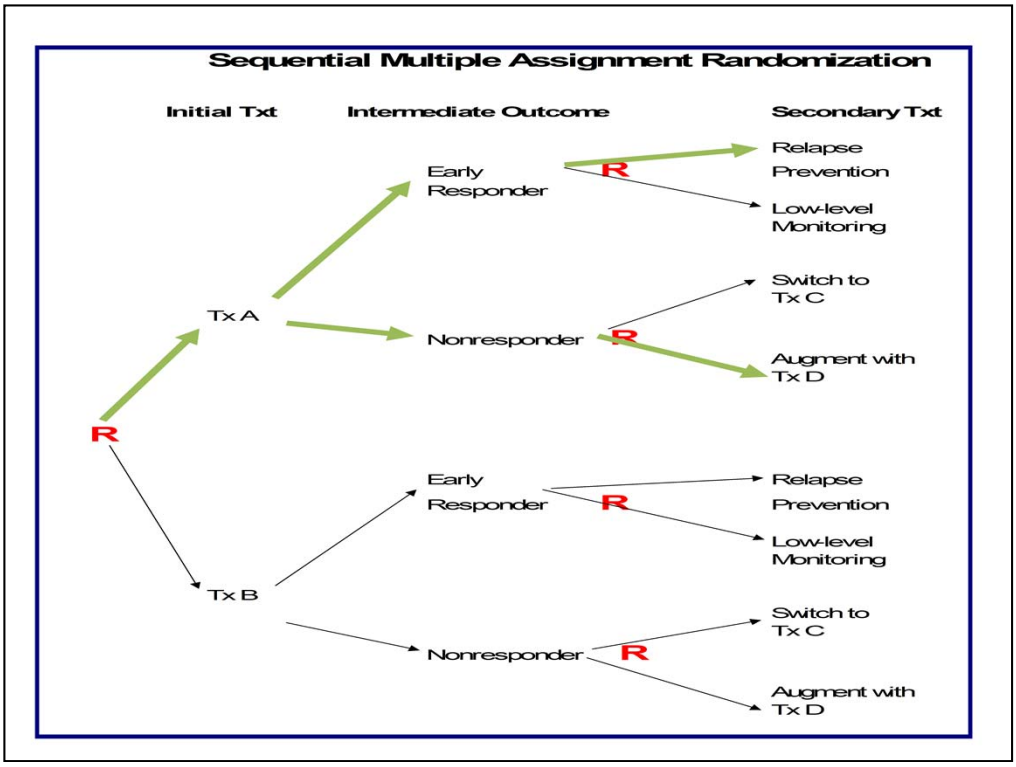
Hypothetical trial: Outcome is not shown but is on far right. The randomizations can take place up front.

Equal randomization

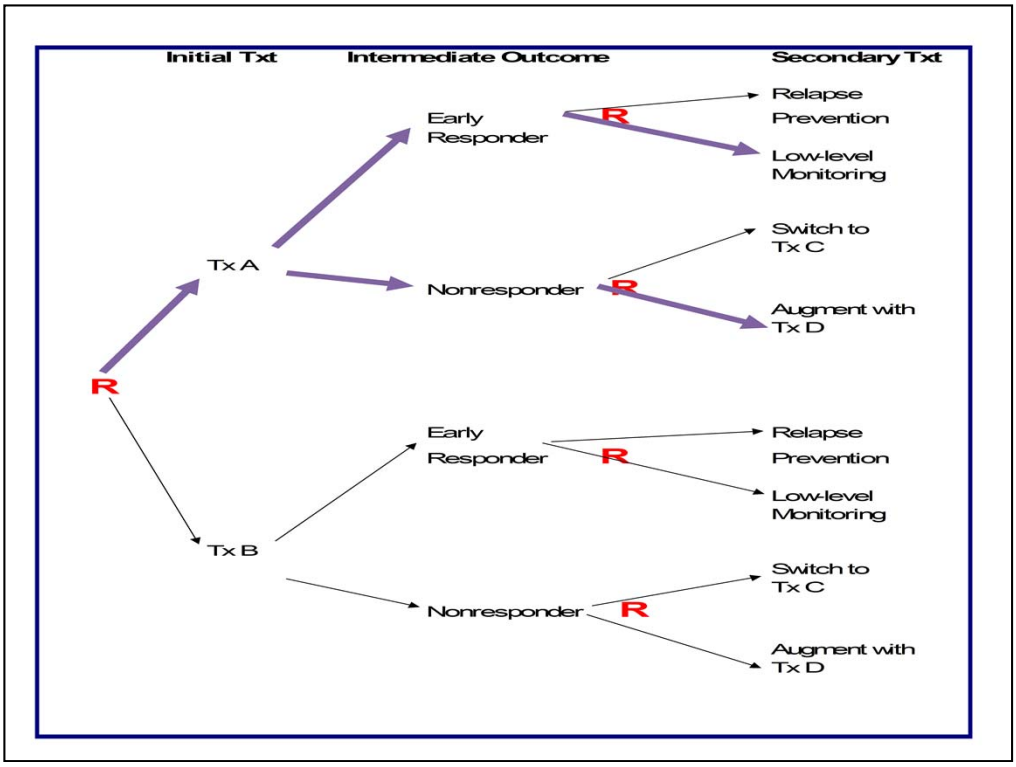
Usual reaction is (1) I'm worried about sample size and

(2) This looks awfully complicated.

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



An embedded adaptive treatment strategy



Another embedded adaptive treatment strategy!

Outline

- What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
- Why SMART experimental designs?
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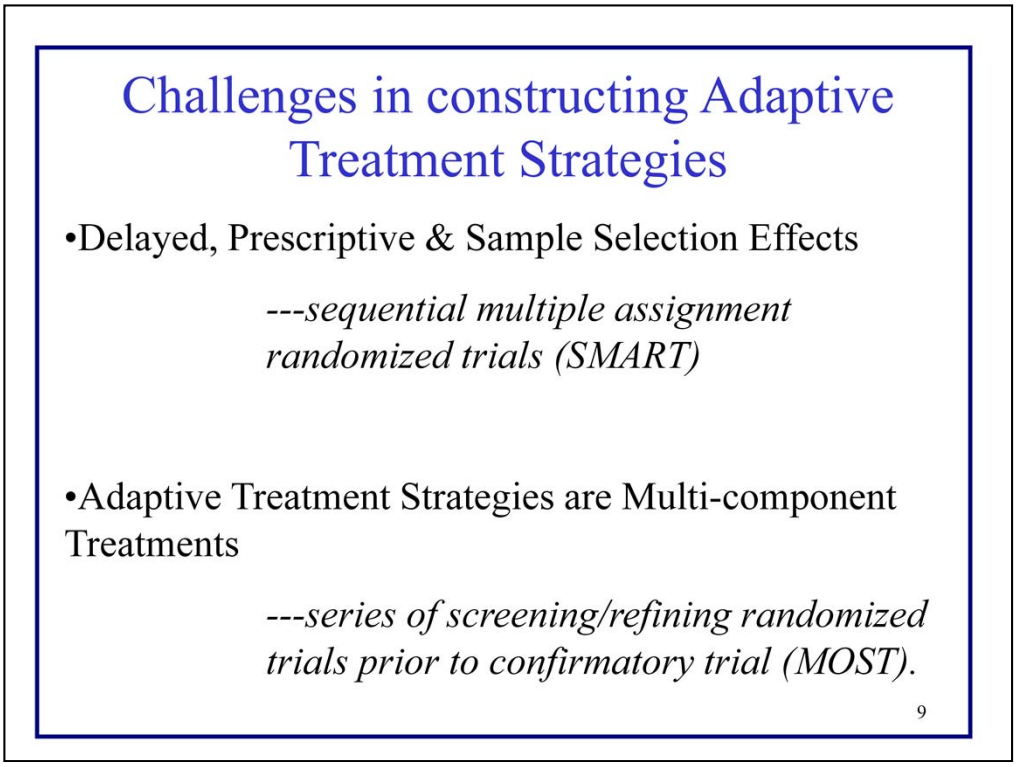


L.M. Collins, S.A. Murphy, V. Strecher (2007). The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent e-Health Interventions. *American Journal of Preventive Medicine* , 32(5S):S112-118

Alternate Approach I to Constructing an Adaptive 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.

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

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.

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 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.

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) 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)
- We want to prevent negative delayed effects.

Harnessing Delayed Therapeutic Effects

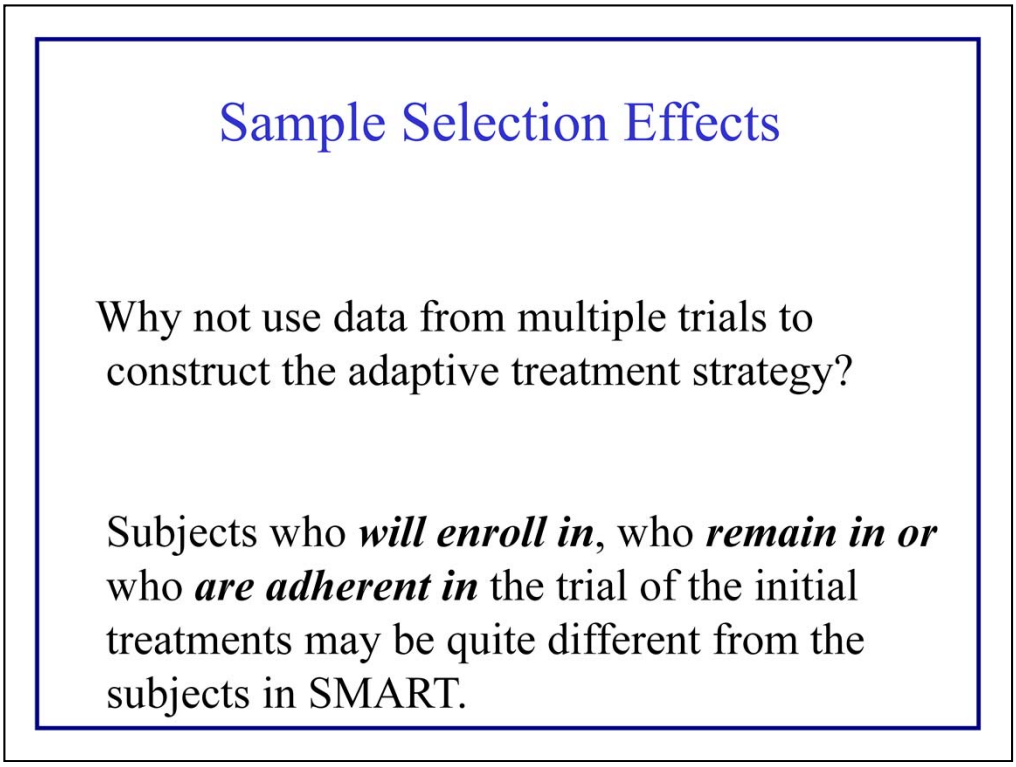
Using data from multiple trials to construct the adaptive treatment strategy is less helpful in harnessing delayed therapeutic effects because we need to assess the combined effect of a sequence of treatments.

Prescriptive Effects

Why not use data from multiple trials to construct the adaptive 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 enhanced 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.

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 Treatment Strategy

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

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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.
- We don't know what components of the adaptive treatment strategy 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

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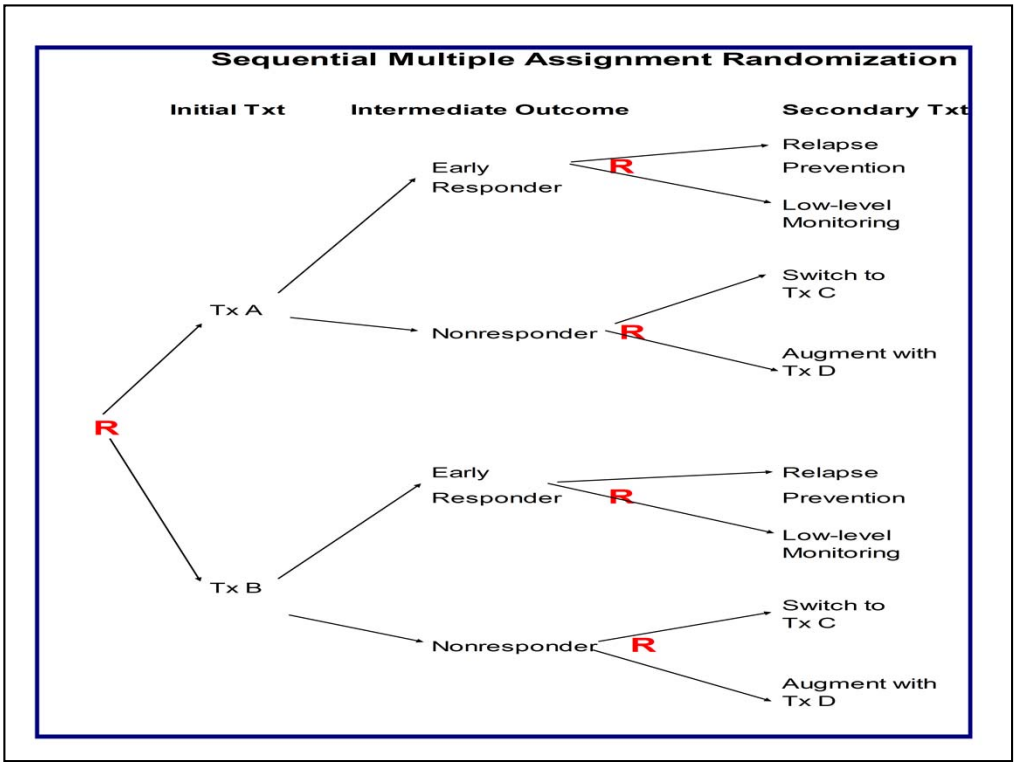
confirmatory trial is to compare the developed adaptive treatment strategy versus an appropriate alternative—this is the standard randomized two group trial.

MOST multistage optimization strategy


Sequential Multiple Assignment Randomization
Initial Txt
Intermediate Outcome
Secondary Txt
R
Tx A
Tx B
Early Responder
Nonresponder
Early Responder
Nonresponder
R
R
R
R
Relapse Prevention
Low-level Monitoring
Switch to Tx C
Augment with Tx D
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

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.

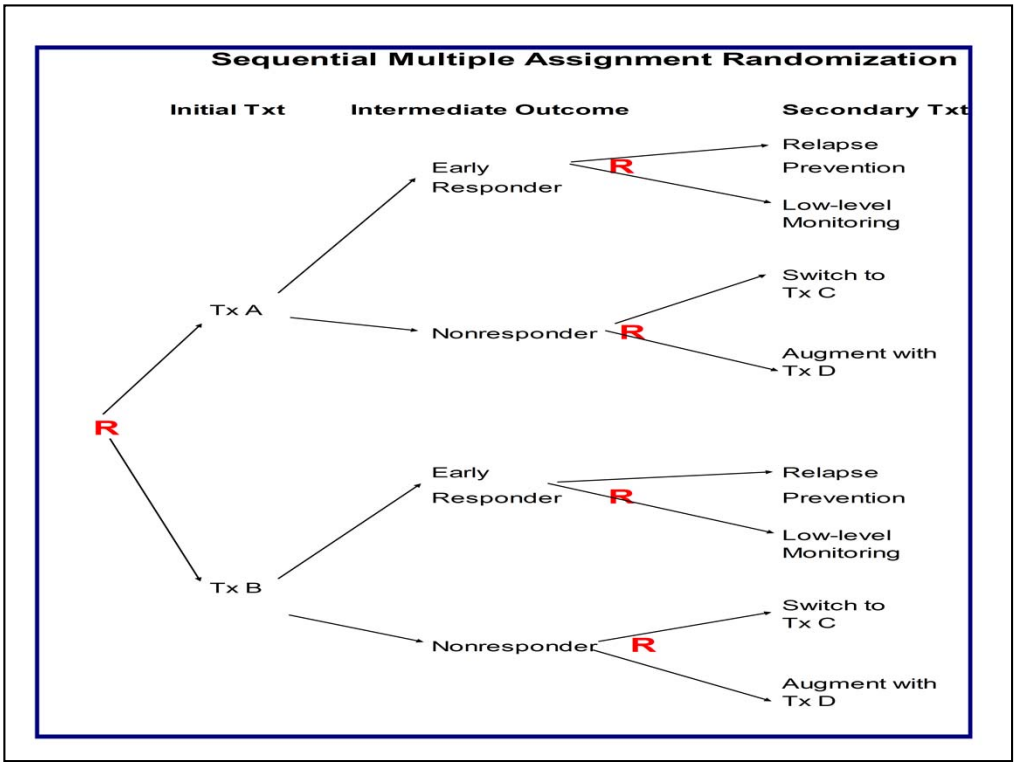
- •This timing decision became one of the critical decisions to investigate.

•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 treatment strategy.

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 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

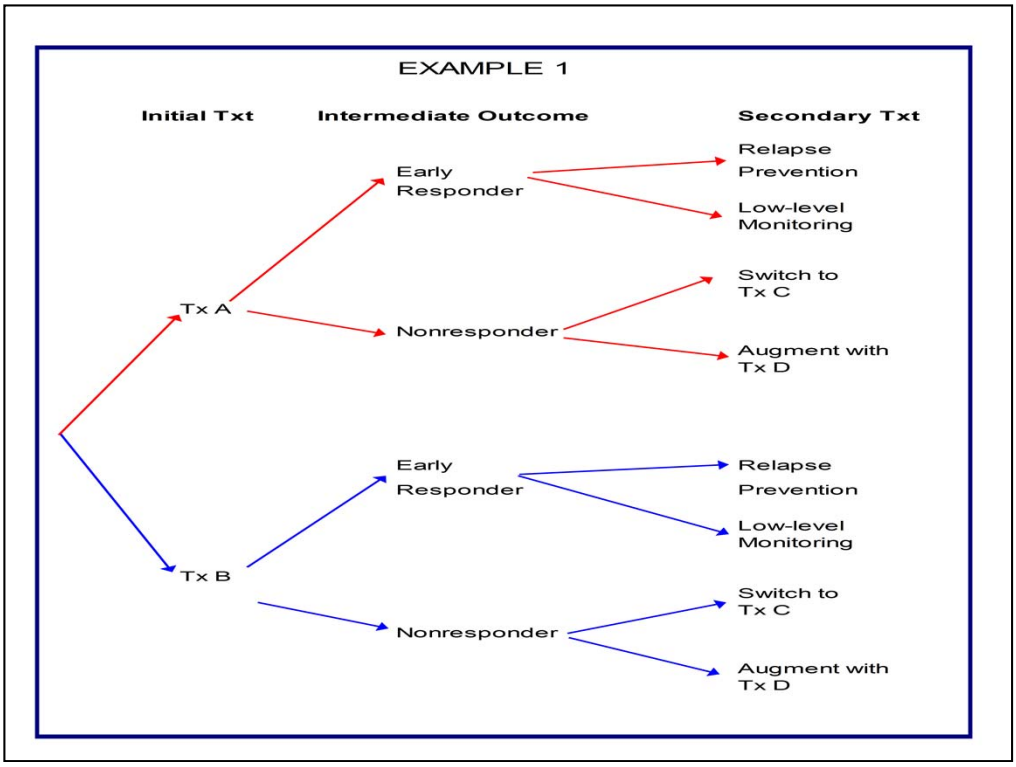
•EXAMPLE 1: (*sample size is highly constrained*): Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

•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

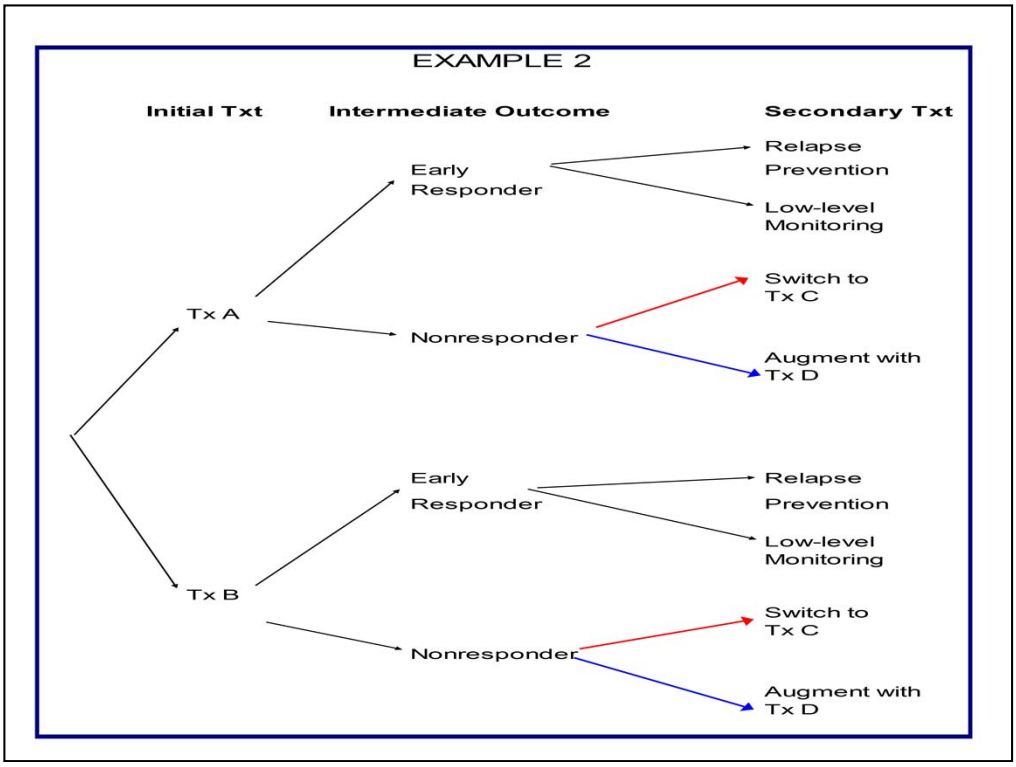
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

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.

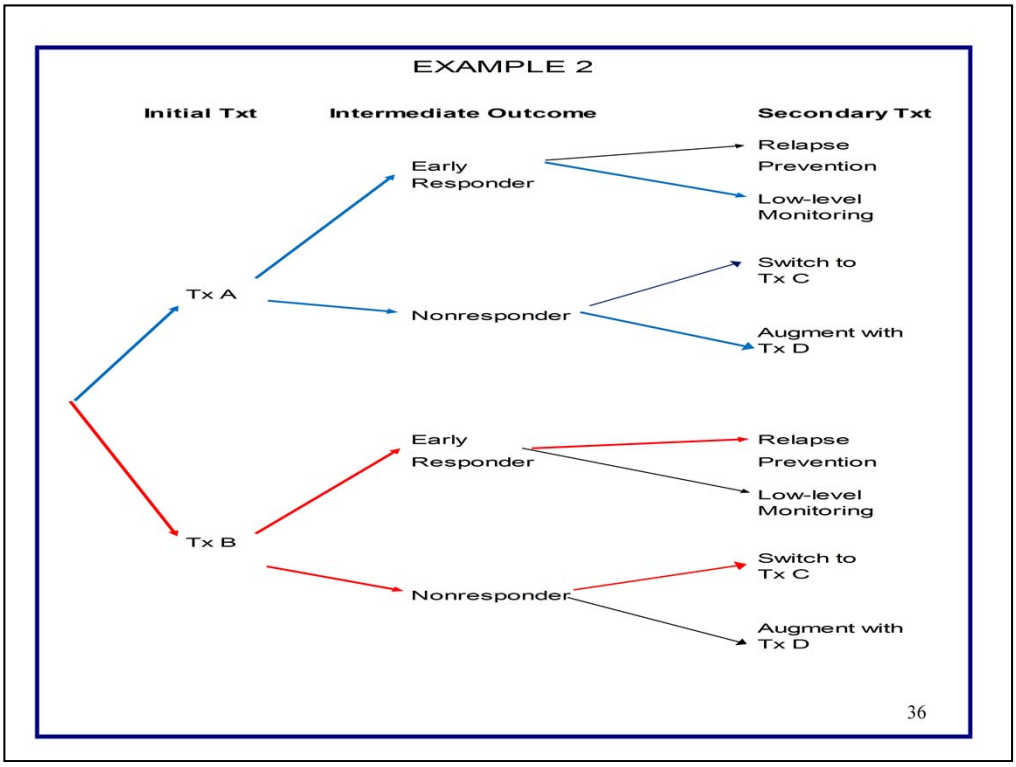


A study of nonresponders in which one controls the tx's to which people don't respond to.

SMART Designing Principles: Primary Hypothesis

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

These are main effects a la' ANOVA



Sample size formula for this SMART to compare the red versus blue embedded adaptive treatment strategies 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

α = .05, power =1 – β=.85

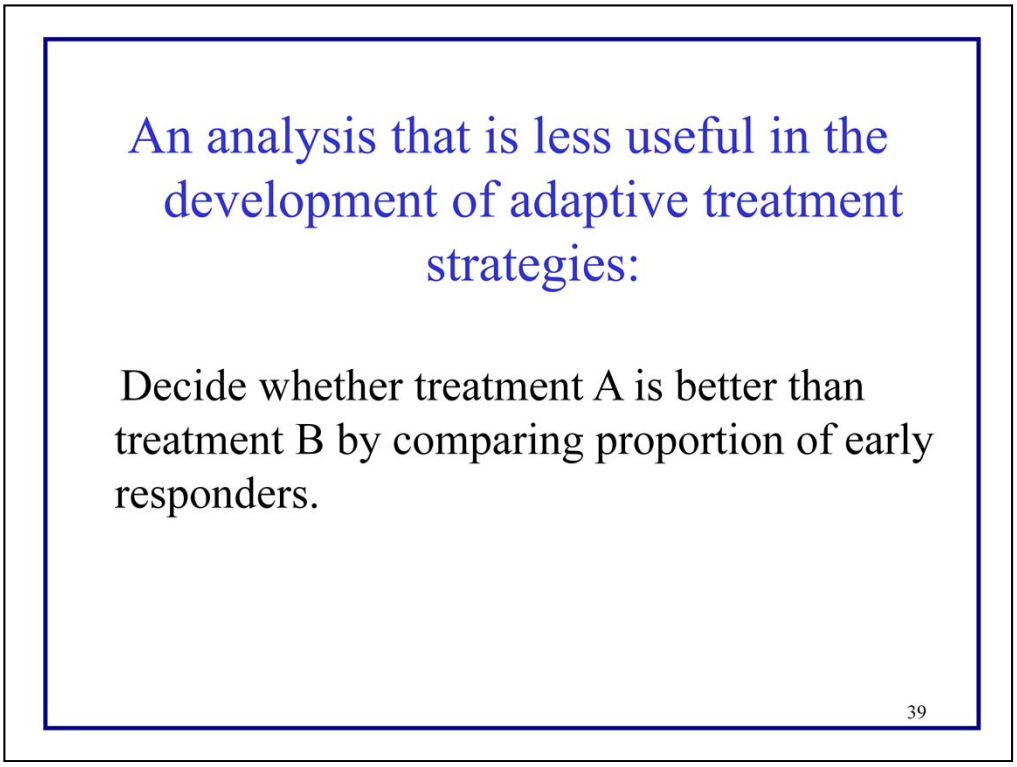
Sigma for example 1 is the std of primary outcome of patients initially assigned tx A (or B)

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

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 treatment strategy (or red adaptive treatment strategy).



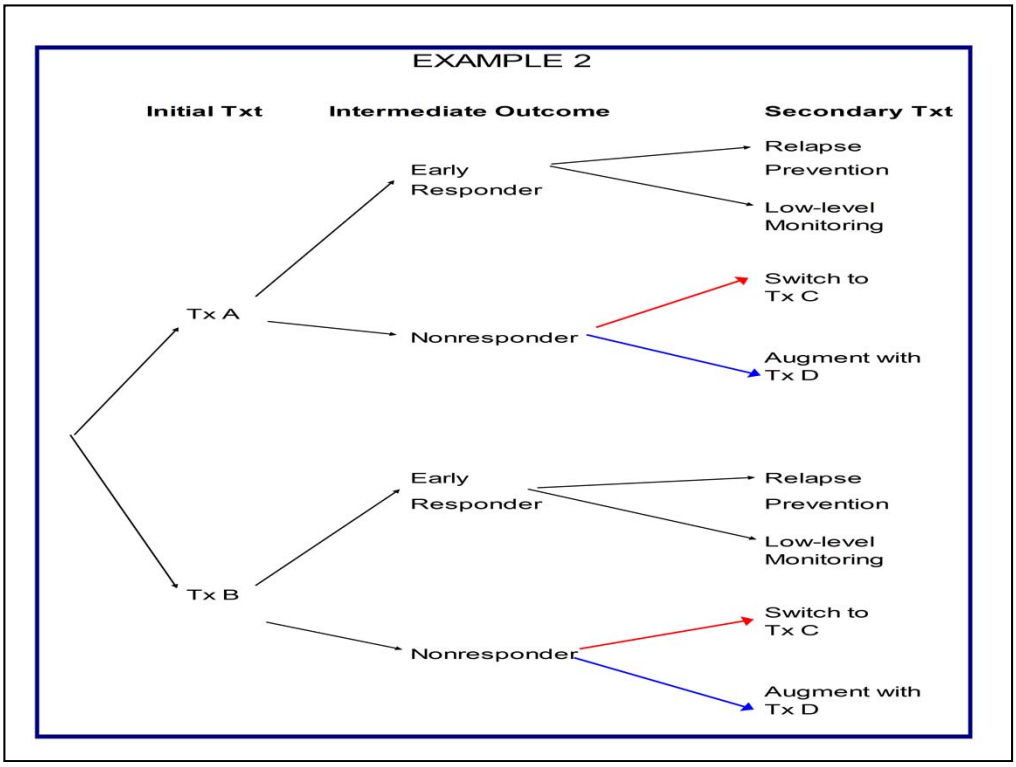
It is interesting but not as useful in the development of adaptive treatment strategies

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.

Summary & Discussion

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

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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. Almiral, 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.