Adaptive Treatment Strategies

Getting SMART About Developing Individualized Sequences of Adaptive Health Interventions

University of Minnesota, June 8

Susan A. Murphy & Daniel Almirall

40 minutes

What are adaptive treatment strategies (ATS)? Give examples of ATSs.

- Discuss why ATSs are needed and how they inform clinical practic e.
- Compare simple ATSs versus more deeply tailored ATSs.

Give examples of ADHD

Outline

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

Other names are dynamic treatment regimes, treatment algorithms, 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

Adaptive Treatment Strategies

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

- Operationalize clinical practice.

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

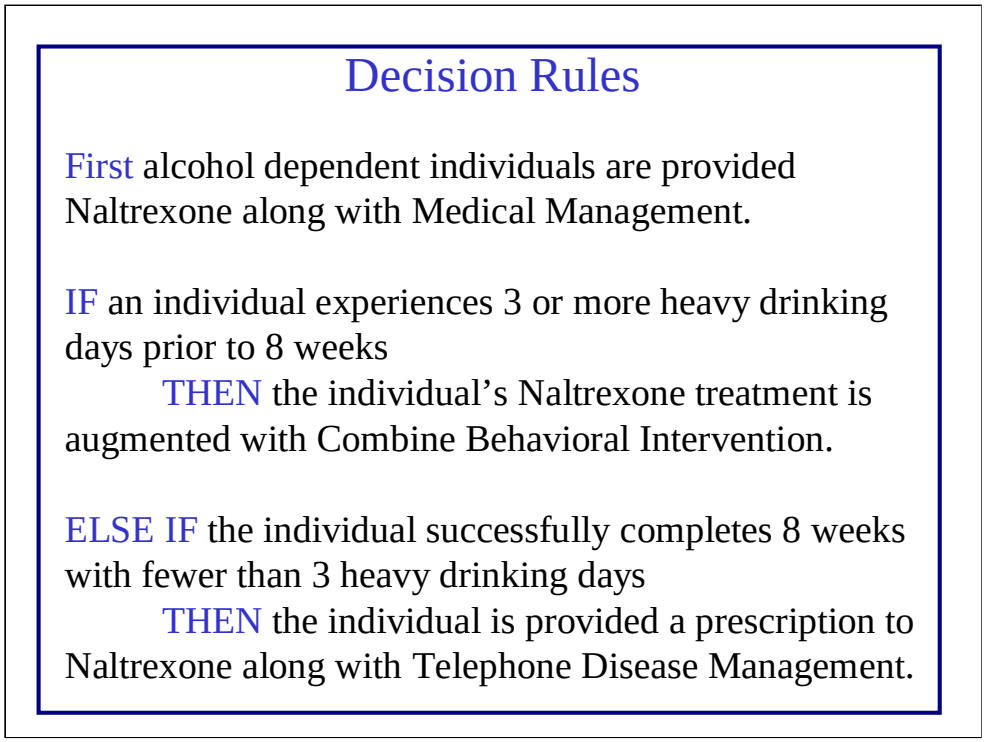
Tailoring is achieved by use of a decision rules. Takes ongoing info (past response,adherence, burden,etc)
and outputs txt level type

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

Adaptive Aftercare for Alcohol Dependent Individuals

- Overall goal: prevent relapse to alcohol abuse
- Critical treatment decisions: which treatment to provide first?; which treatment to provide second?
- Tailoring variable: heavy drinking days

These individuals graduated from an Intensive Outpatient program.



Stepping up txt:

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

What does decision rule do?

When to start txt, when to stop txt, when to change txt, what txt to change to

Adaptive Treatment Strategies

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

- From the clinical scientist's point of view: a sequence of decision rules that recommend one or more treatments at each critical decision.

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

The design of the adaptive treatment strategy is a multi-stage decision problem.

Also how to combine therapies?

More examples of critical treatment decisions and tailoring variables

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

• Tailoring variables: severity of illness, presence of comorbid mental or physical conditions, family support, adherence to present treatment, side effects resulting from present treatment, symptoms while in treatment.

Other tailoring variables are genetics, family background, proteomics

Another Example of an Adaptive Treatment Strategy

- Adaptive Drug Court Program for drug abusing offenders.
- Goal is to minimize recidivism and drug use.
- Marlowe et al. (2008)

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

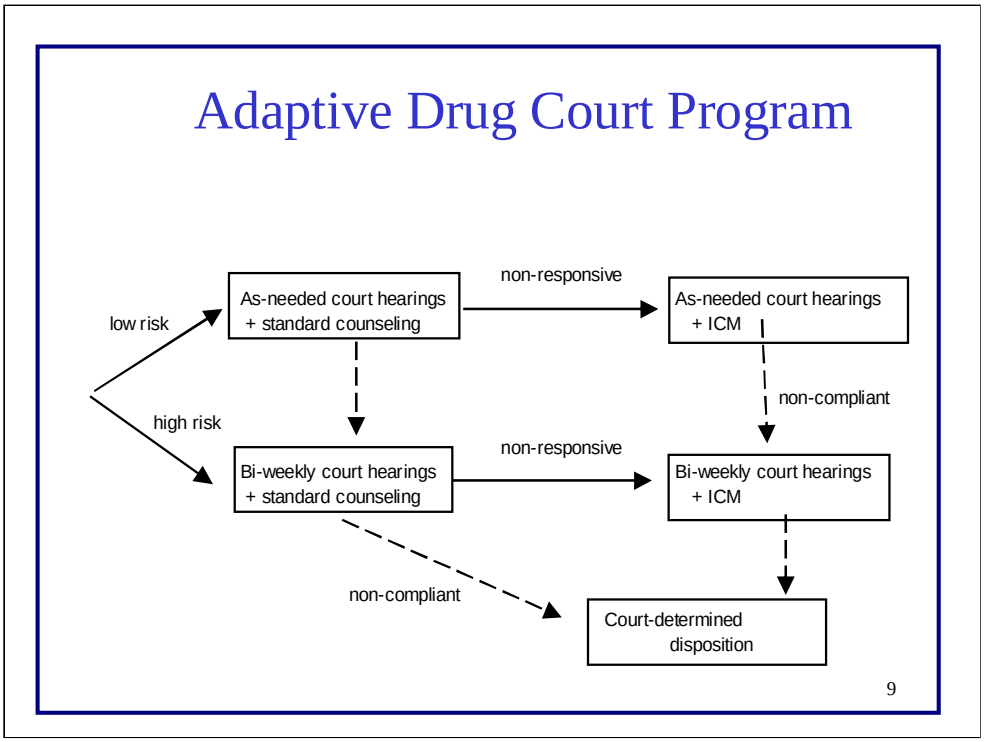
minimize recidivism and drug use is operationalized by graduating from the drug court program.

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

Noncompliance: is(1) falls below threshold for attendance in counseling sessions or status hearings, (2) fails to provide scheduled urine specimens, **or** (3) commits a new crime or serious rule infraction

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

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



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Adaptive Interventions in Drug Court: A Pilot Experiment

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

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 below threshold for attendance in 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.

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

Other Examples of Adaptive Treatment Strategies

- Brooner et al. (2002, 2007) Treatment of Opioid Addiction
- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008) Drug Court
- Rush et al. (2003) Treatment of Depression

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

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

The decision rules used by Brooner et all, Marlowe 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 losely 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.

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Why Adaptive Treatment Strategies?

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

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

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

Why Adaptive Treatment Strategies?

2) Chronic or Waxing and Waning Course

Improvement often marred by relapse

Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient

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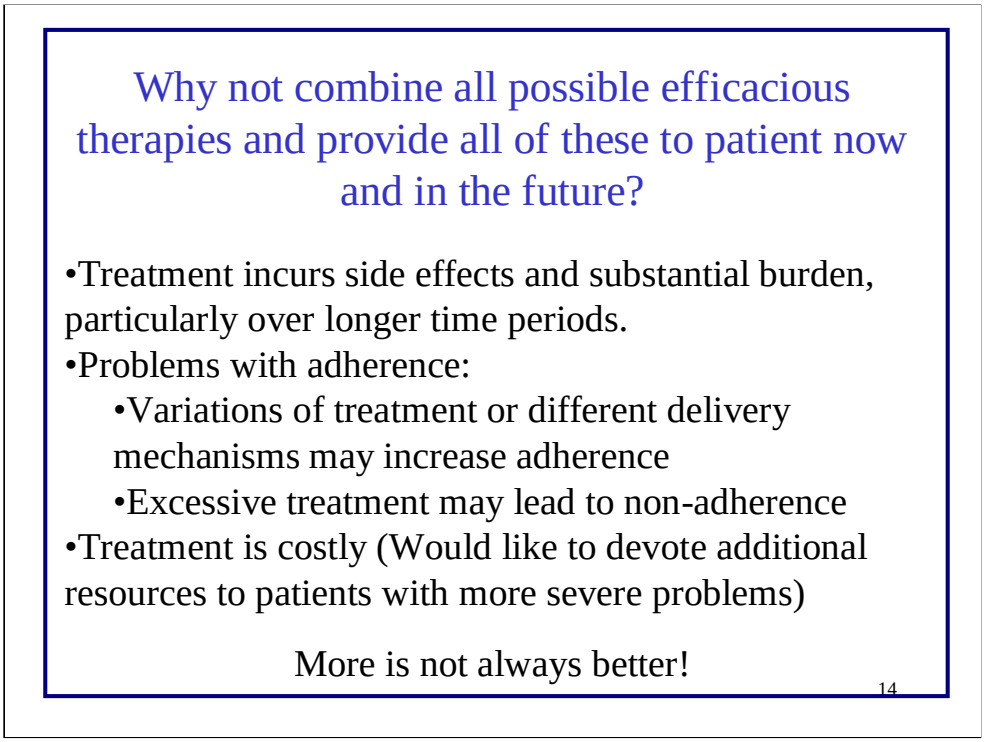

Why not give a universal intervention to all for a sufficiently long time??

More is not always better.

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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Treatment Design Goals

•Maximize the strength of the adaptive treatment strategy

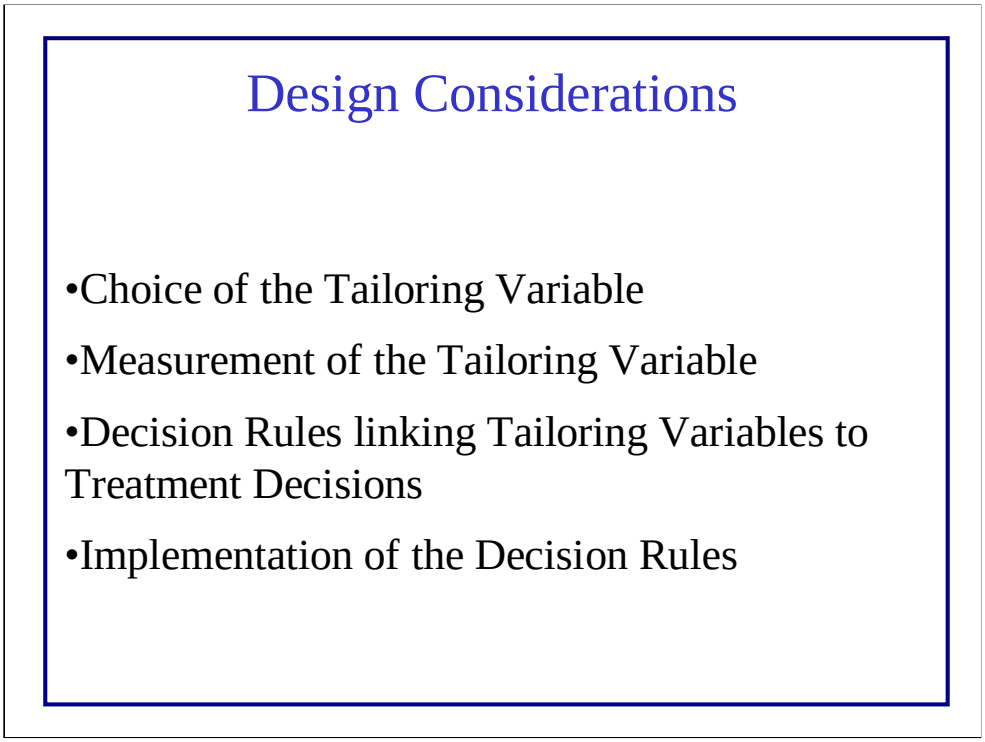
- by well chosen tailoring variables, well measured tailoring variables, & well conceived decision rules

CLARIFICATION NOTE: Here we are discussing the design of the adaptive treatment strategy (hence "treatment design"). We are not discussing the design of a trial to inform the development of an ATS—that's the next module on "trial design".

Treatment Design Goals

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

To achieve this goal, ATS should be explicit.



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

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

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

This bundle denotes one txt. Condition

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 varies by individual characteristics.

Adaptive Aftercare for Alcohol Dependent Individuals

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

tailoring variable: heavy drinking proximal outcome!

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

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

Suppose we took people on naltrexone and randomized some to cbi and others to no cbi. Then we expect that the effect of cbi will be positive for individuals who have returned to heavy drinking and will be nonexistent or negative for individuals who are maintaining a non-drinking lifestyle.

Technical Interlude!

s=tailoring variable

t=treatment type (0 or 1)

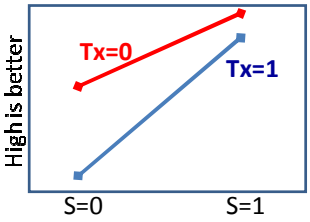
Y=primary outcome (high is preferred)

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

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

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

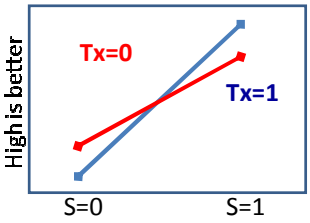
BAD



S is a moderator variable because the magnitude of the effect of Tx=1 versus Tx=0 differs by levels of S.

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

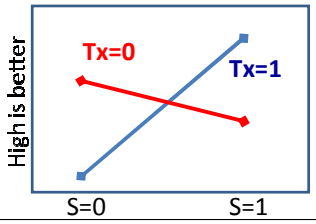
BETTER



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

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

BEST



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

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

Measurement of Tailoring Variables

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

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 and from collaterals is not weekly –oh no!.

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

Biological: Carbohydrate Deficient Transferrin (CDT).

Derivation of Decision Rules

- Articulate a theoretical model for how treatment effect on key outcomes should differ across values of the moderator.
- Use prior clinical experience.
- Use prior experimental and observational studies.
- Discuss with research team and clinical staff, "What dosage would be best for people with this value on the tailoring variable?"

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.

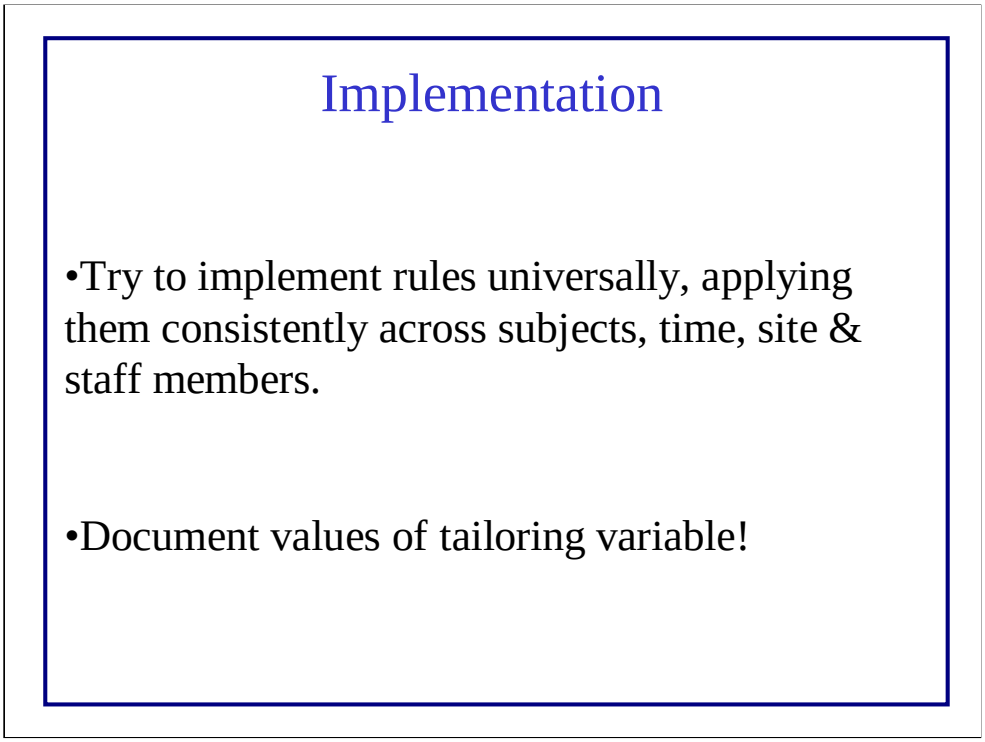
Derivation of Decision Rules

- 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.

Greater than 1 heavy drinking day within a two month period.

In weeks 3-8 can be declared a nonresponder and switched to NTX+MM+CBI



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. The non systematic component of these factors introduces random error into the treatment, thereby lessening its effectiveness. The systematic component of these factors harms replicability by introducing confounders into the experimental comparison of the preventive intervention with other conditions. That is we have alternate explanations for txt effect.

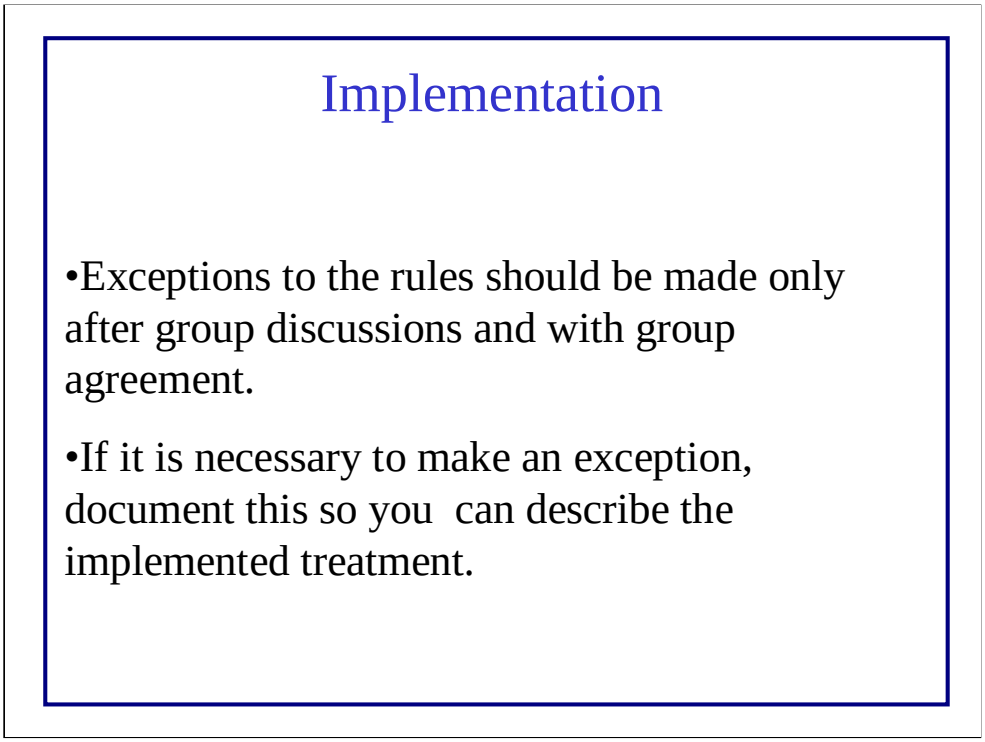
Staff perceive dosage rules are inappropriate in a particular case

missing needed tailoring variables, measure of tailoring variable lacks validity, the way the tailoring variable weighs different criteria may be questioned.

Rules are stated ambiguously or staff person is insufficiently trained.

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.



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.

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

Txt bundle effect should be robust to context, family, individual characteristics

Do this by making txt rules sensitive to context, family individual characteristics.

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

Summary & Discussion

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

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

A Dynamic Bayesian Network to evaluate the performance of Intensive Care Units.

Davide Luciani, MD

John Rust has a good bit of work in econometrics that assumes expert knowledge and then finds best decision rules.

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 down 2-3 simple ATSs to address a chronic disorder in your field!

Next up!: Experimental Study designs for use in finding good tailoring variables and rules.

Sequential, Multiple Assignment, Randomized Trials

Getting SMART About Developing Individualized Sequences of Adaptive Health Interventions

University of Minnesota, June 8

Susan A. Murphy & Daniel Almirall

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 Trials (SMARTs)?
- Why SMART experimental designs?
- Trial Design Principles
- Examples of SMART Studies
- Summary & Discussion

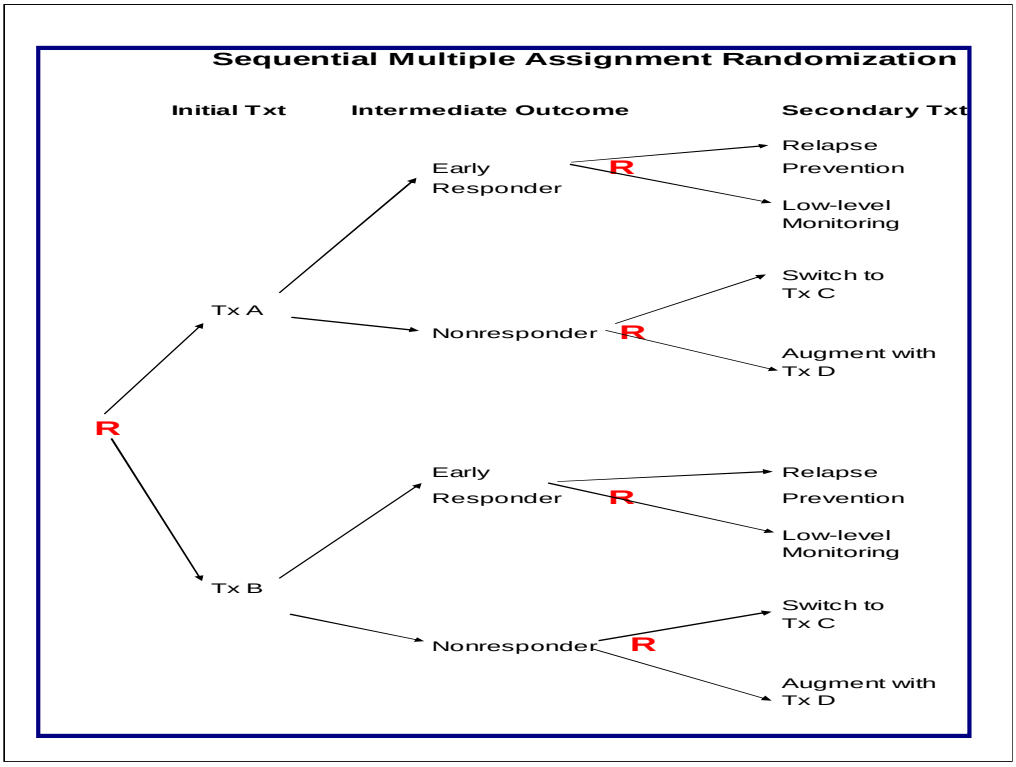
What is a SMART Study?

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)



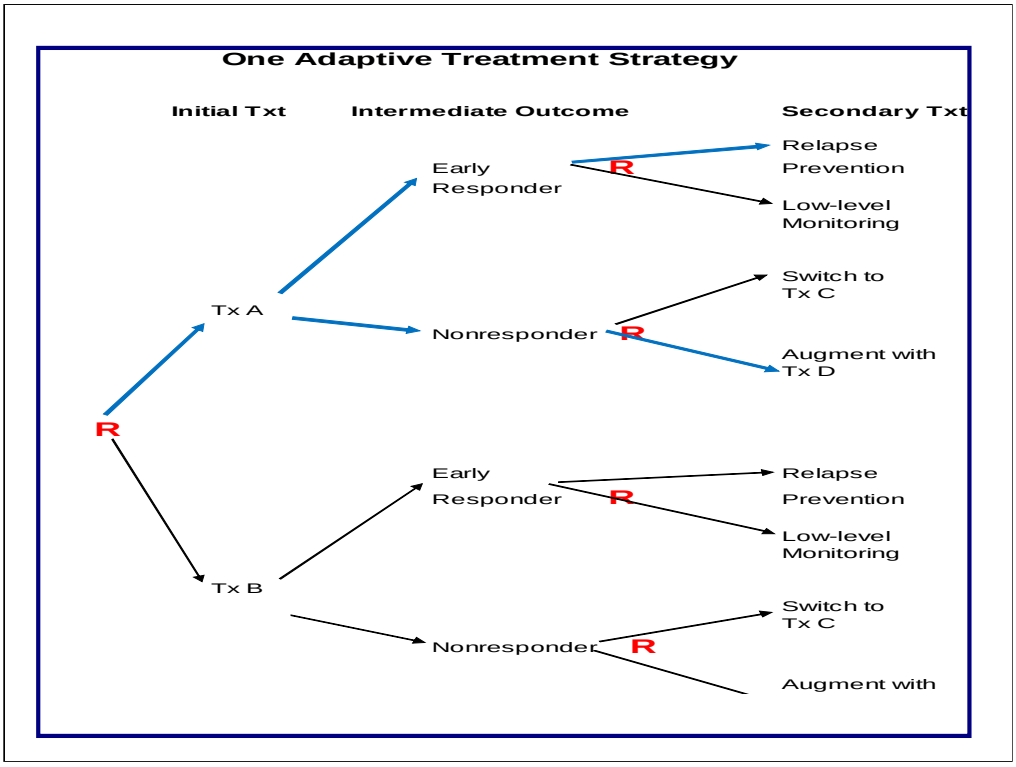
Hypothetical trial: Outcome is not shown but is on far right. The randomizations can take place up front.

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

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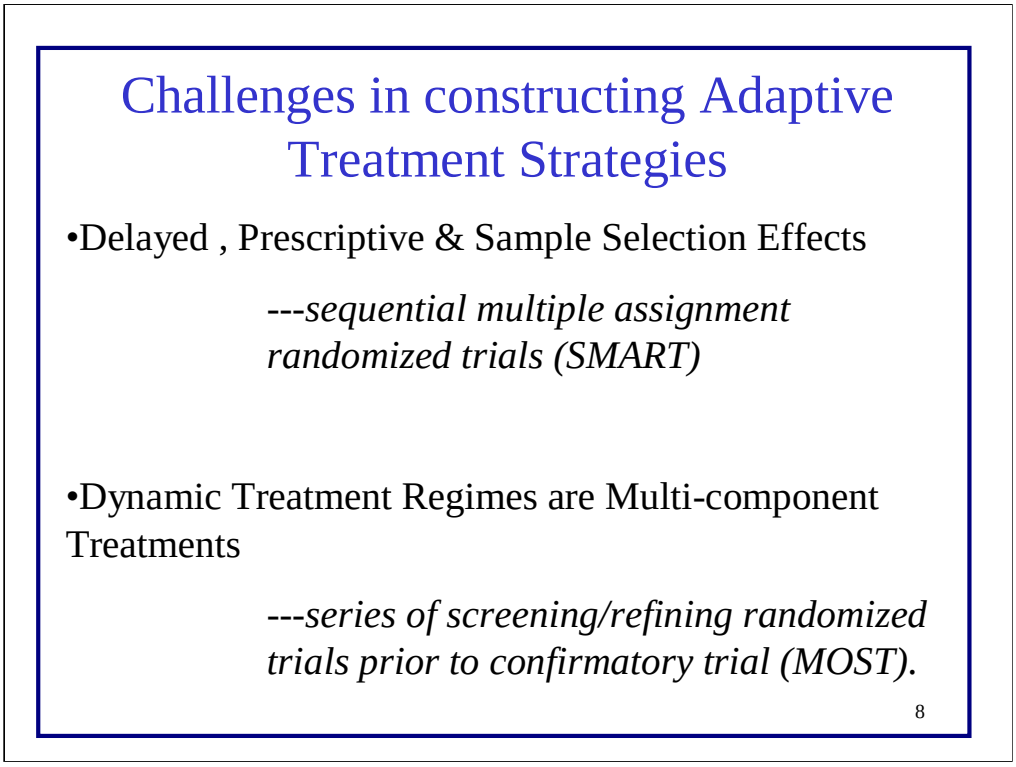

L.M. Collins, S.A. Murphy, V. Strecher (2007). The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New Methods for More Potent e-Health Interventions. *American Journal of Preventive Medicine* , 32(5S):S112-118

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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.

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 one of several maintenance therapies based on longer term 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!!!

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), 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.

Sample Selection Effects

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

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

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 especially if the subject doesn't know if they are receiving treatment such as in a double bind study. 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

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?

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Don't know why your treatment regime 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?

Why constructing a dynamic treatment regime and then comparing the regime against a standard alternative is not always the answer.

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

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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

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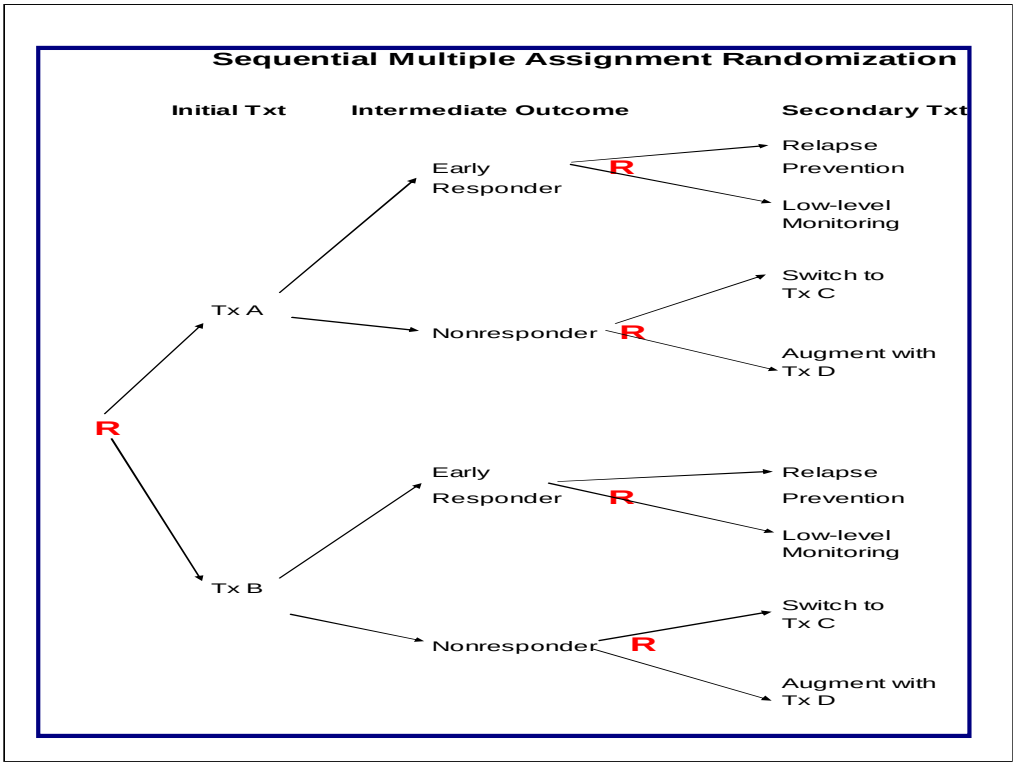
confirmatory trial is to compare the developed adaptive treatment strategy versus an appropriate alternative—this is the standard randomized two group trial.

MOST multistage optimization strategy



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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

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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 aids in developing the adaptive treatment strategy.

- •Power trial to address these hypotheses.

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

- •Trial is not necessarily powered to address these hypotheses.

SMART Designing Principles: Primary Hypothesis

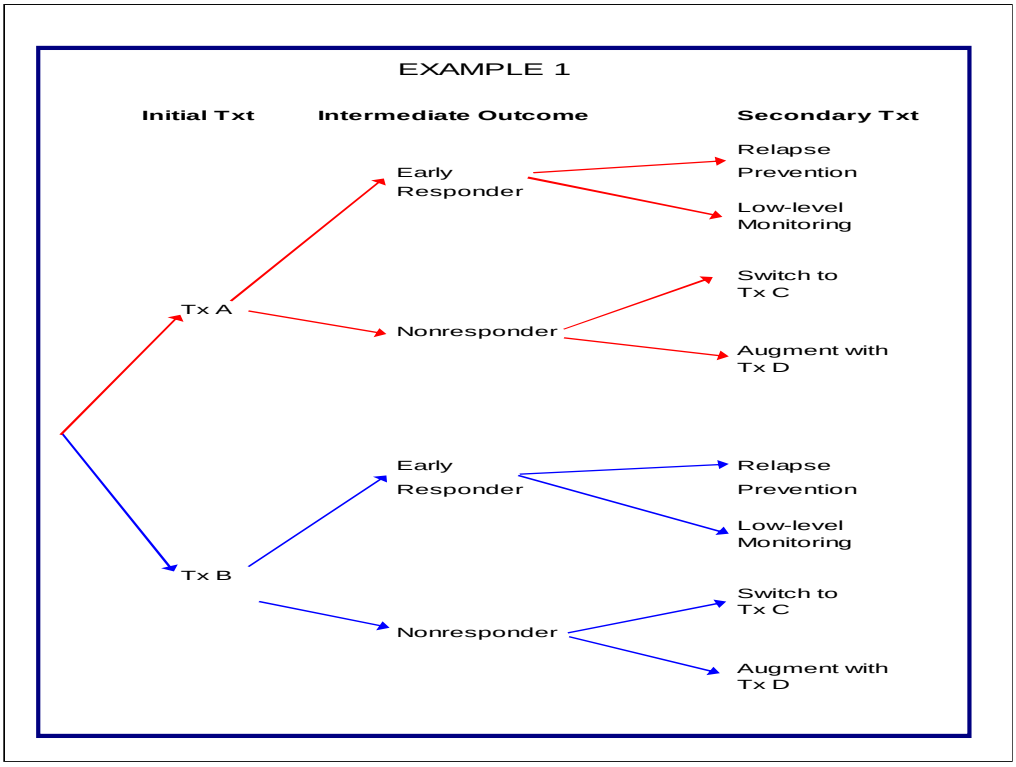
•EXAMPLE 1: (*sample size is highly constrained*): Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

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

These are main effects a la' ANOVA

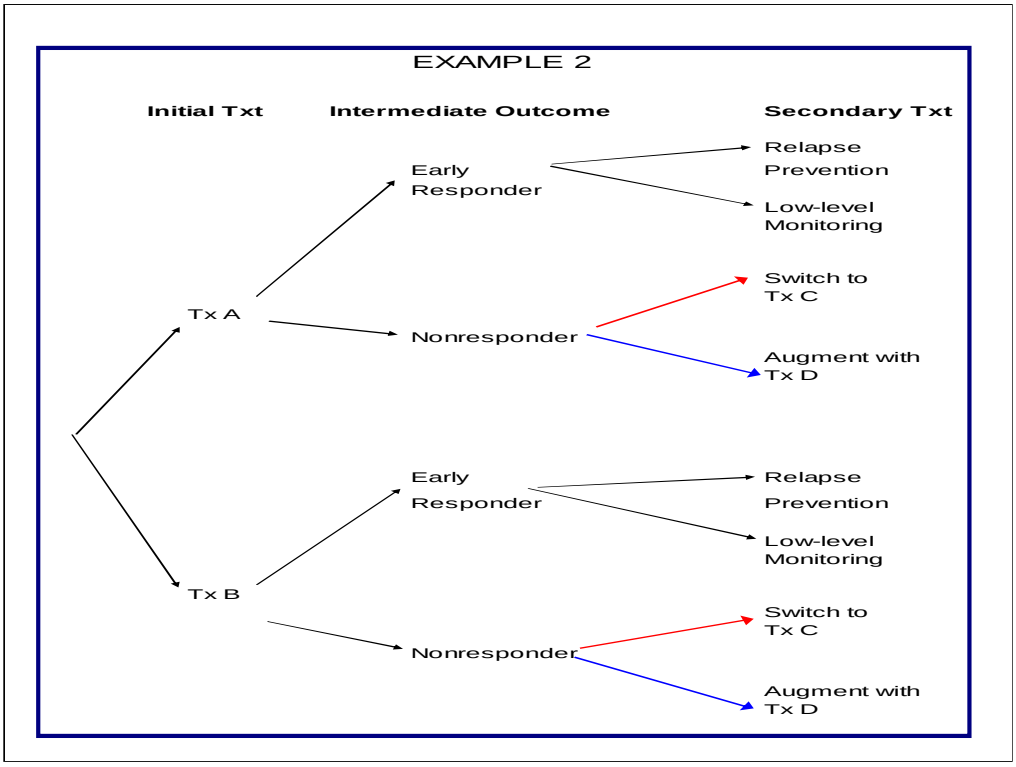
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

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

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

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).

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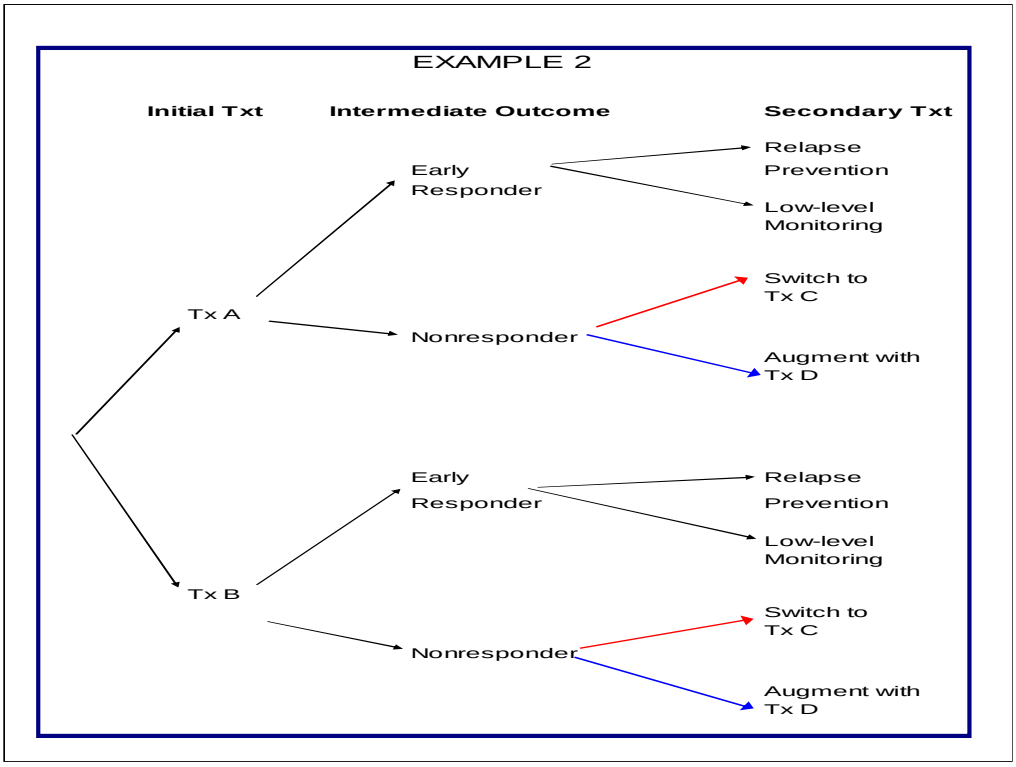
SMART Designing Principles

•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

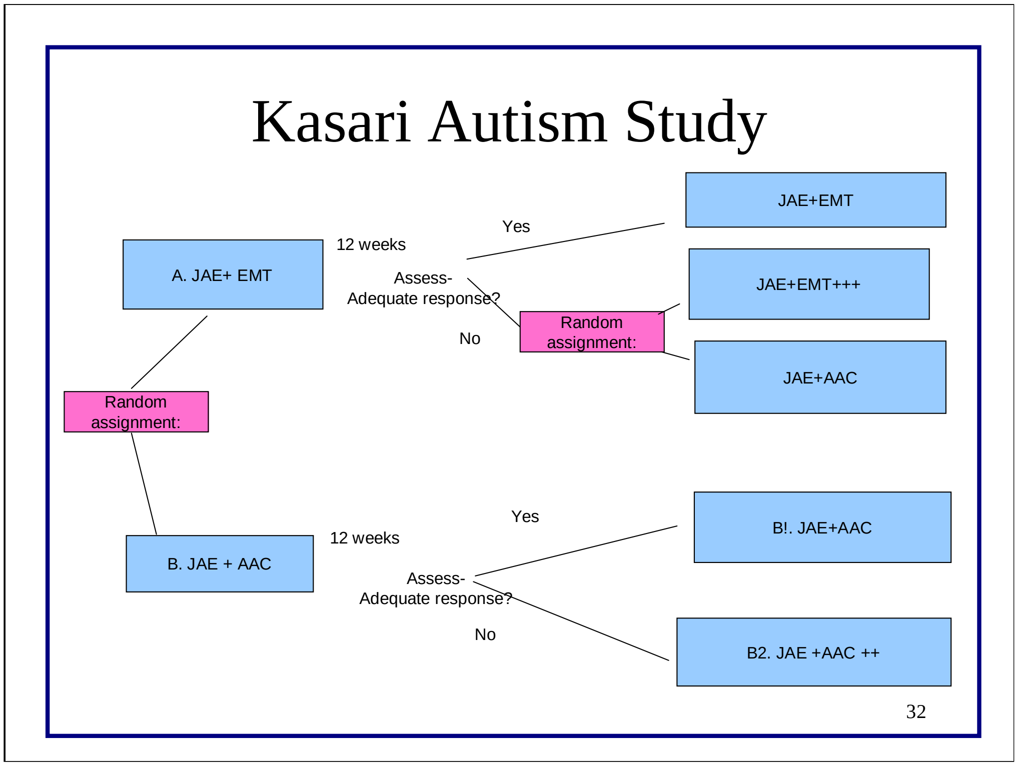
Use analysis of covariance or regression.



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.

Outline

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



Pop'n: children who are nonverbal (not

using spoken language) by 5 years of age despite involvement in traditional intervention programs

N=90

cutoff for nonresponse at 12 weeks is under development (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 half of 12 assessment measures

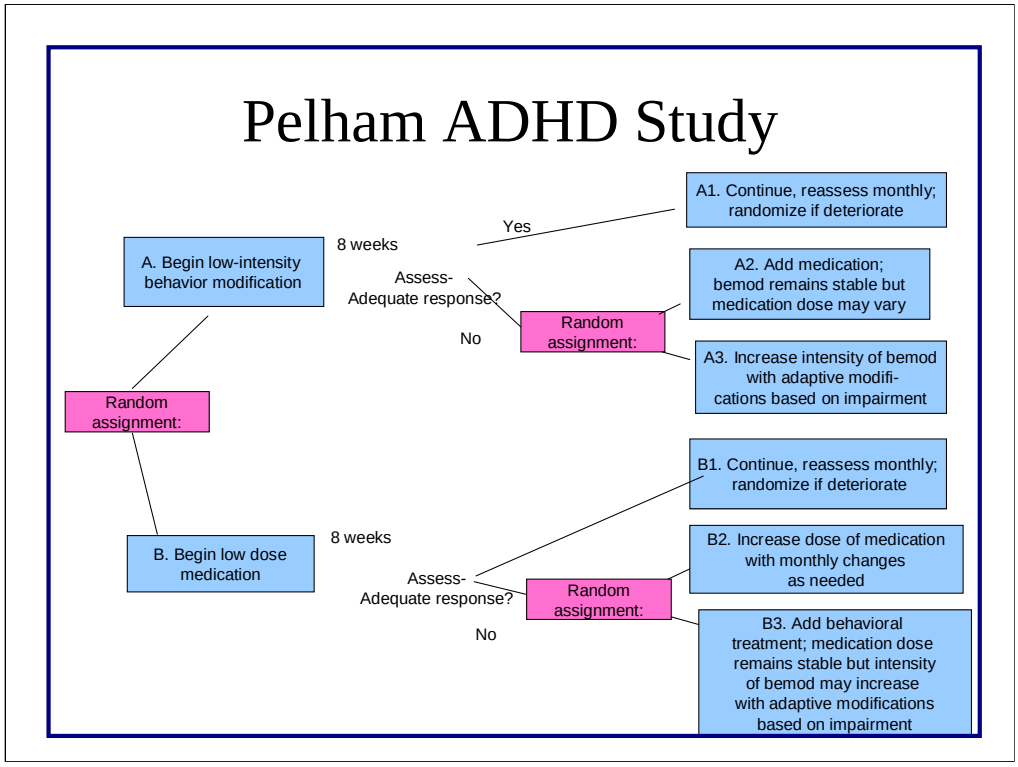
JAE *Joint attention and joint engagement*

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.



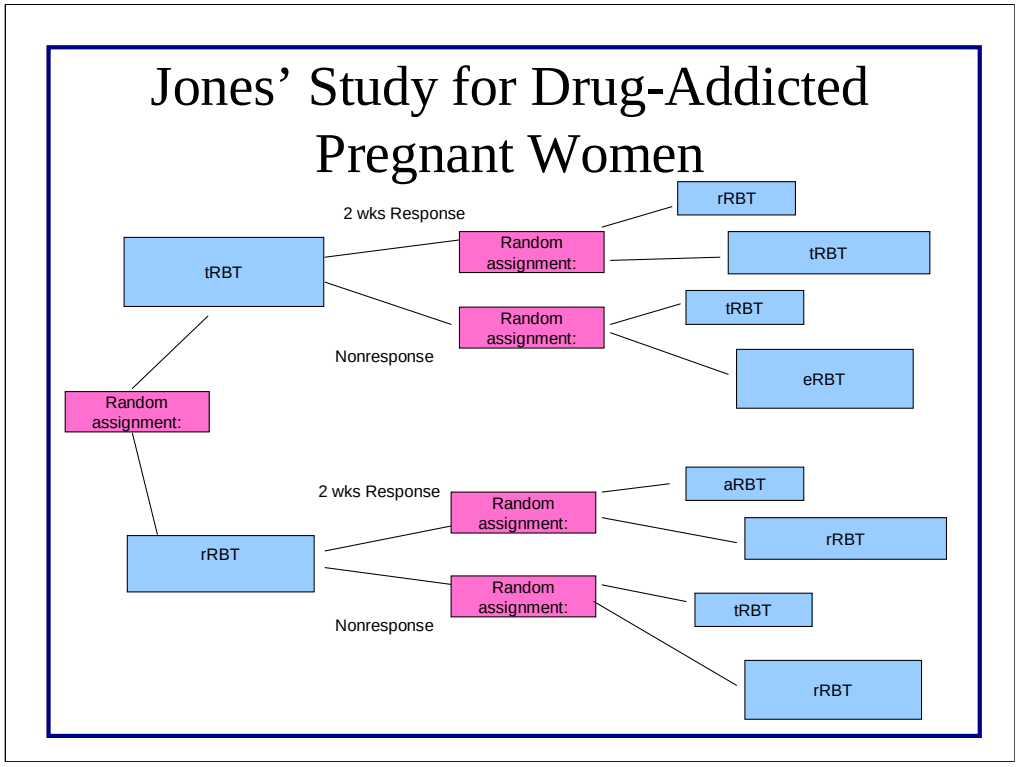
We are analyzing this data

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 measur 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

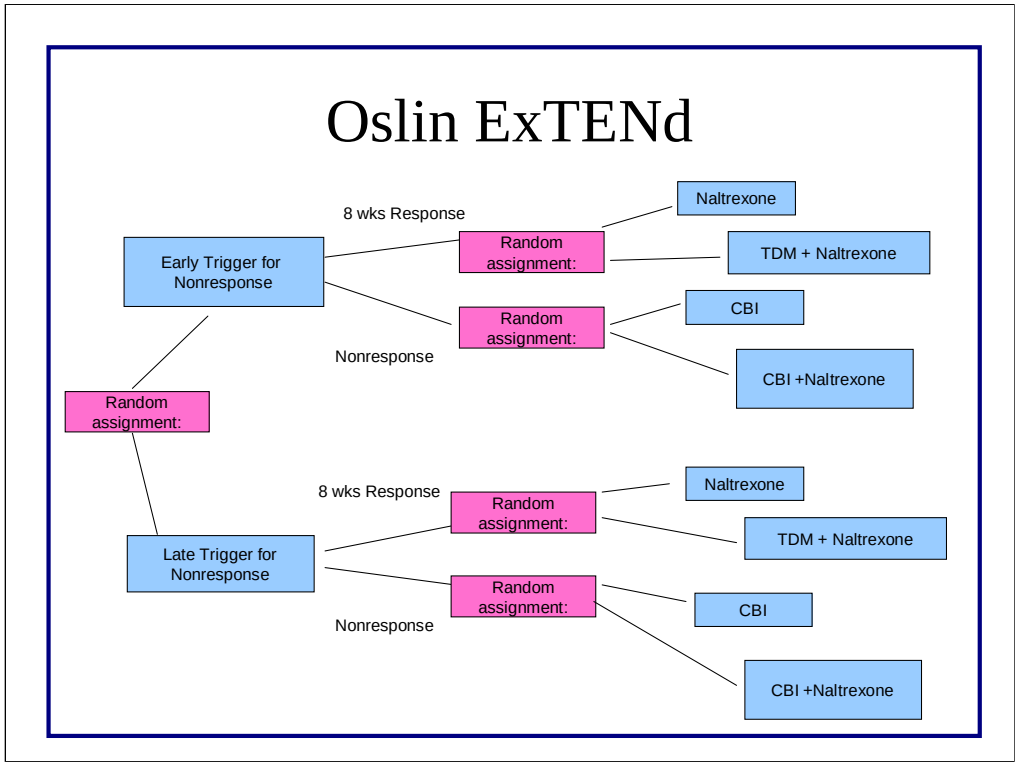
RBT==reinforcement based tx

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 δ 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

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Questions?

More information

S.A. Murphy (2005), An Experimental Design for the Development of Adaptive Treatment Strategies., *Statistics in Medicine*. 24:1455-1481.

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

Nahum-Shani, M. Qian, D. Almiral, W.. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2010). Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. *Technical Report, 10-108*, The Methodology Center, The Pennsylvania State University

Very technical:

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

Practice Exercise

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

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