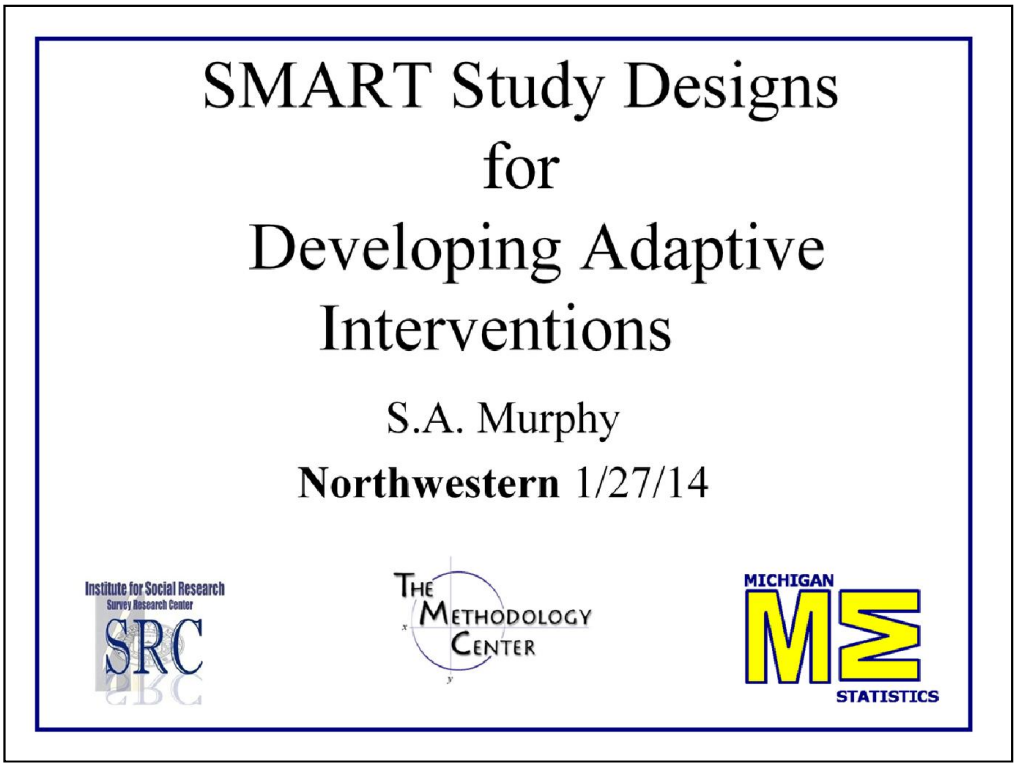

50 min. SMART Study Designs for Developing Adaptive Interventions

Title: SMART Study Designs for Developing Interventions

Abstract:
The effective treatment and management of many behavioral and health disorders often requires individualized, sequential decision making, in which the intervention is dynamically adapted over time based on an individual's changing course. Adaptive interventions operationalize individualized, sequential, decision making via a sequence of decision rules that specify whether, how, for whom, and when to alter the intensity, type, or delivery of psychosocial, behavioral, and/or pharmacological treatments. In this talk, we discuss how a novel, experimental design-sequential multiple assignment randomized trials (SMART) and data analysis methods can be used in the development and optimization of adaptive
interventions. The data analysis method is illustrated using data from the "Adaptive Interventions for Children with ADHD" trial (W. Pelham, PI).

Outline

- Adaptive Interventions
- SMART Designs
- Trial Design Principles and Analysis
- Exploring Individualization using the "Adaptive Interventions for Children with ADHD" study (W. Pelham, PI).

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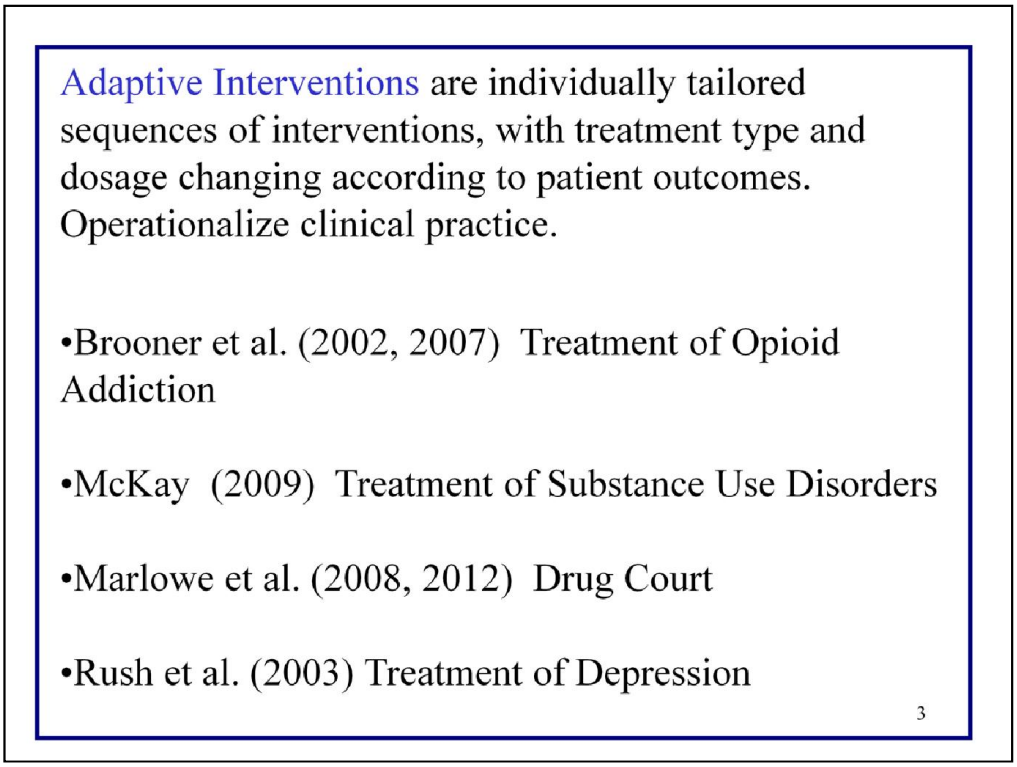
Other names are dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive treatment strategy, treatment protocols. Structured treatment interruptions in the treatment of AIDS were an early form of an adaptive intervention



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 info (genetics, past response,adherence, burden,etc) and outputs txt level type

Most clinical scientists develop the decision rules using trial and error;
developmental and behavioral theories; clinical experience

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

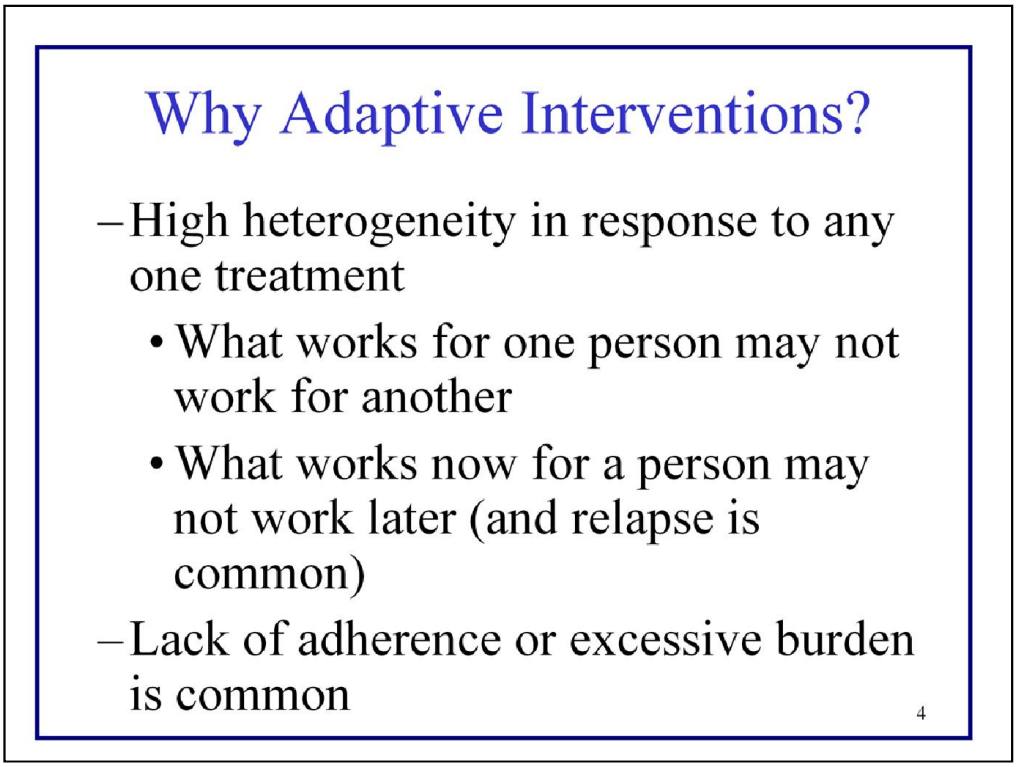
One steps up/down behavioral contingencies based on adherence to counseling sessions.

Rules are explicit.

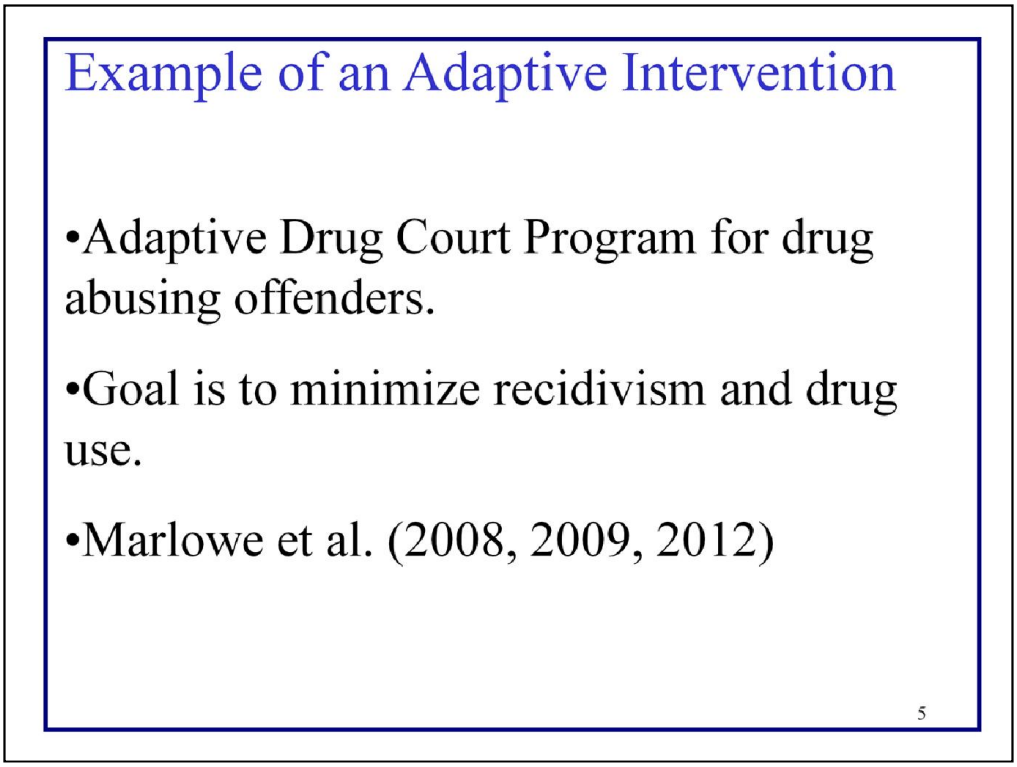
McKay has a book on this topic– see Treating Substance Use Disorders With Adaptive Continuing Care (Hardcover)

by James R. McKay

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.



These are all reasons why we need to plan ahead because we are likely to need to use a sequence of treatments



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.

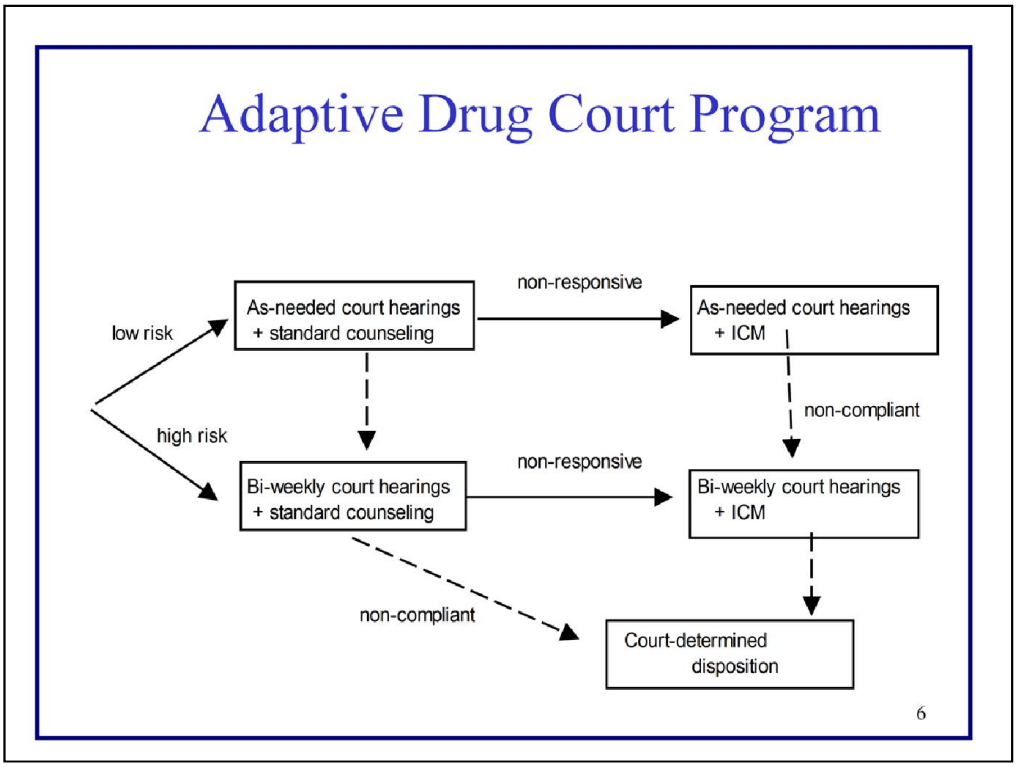
Curr Psychiatry Rep. 2009 Oct;11(5):370-6.

Adaptive Programming Improves Outcomes in Drug Court : An Experimental Trial

Criminal Justice and Behavior 2012 39: 514 Douglas B. Marlowe, David S. Festinger, Karen L. Dugosh,

Kathleen M. Benasutti, Gloria Fox and Jason R. Croft

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

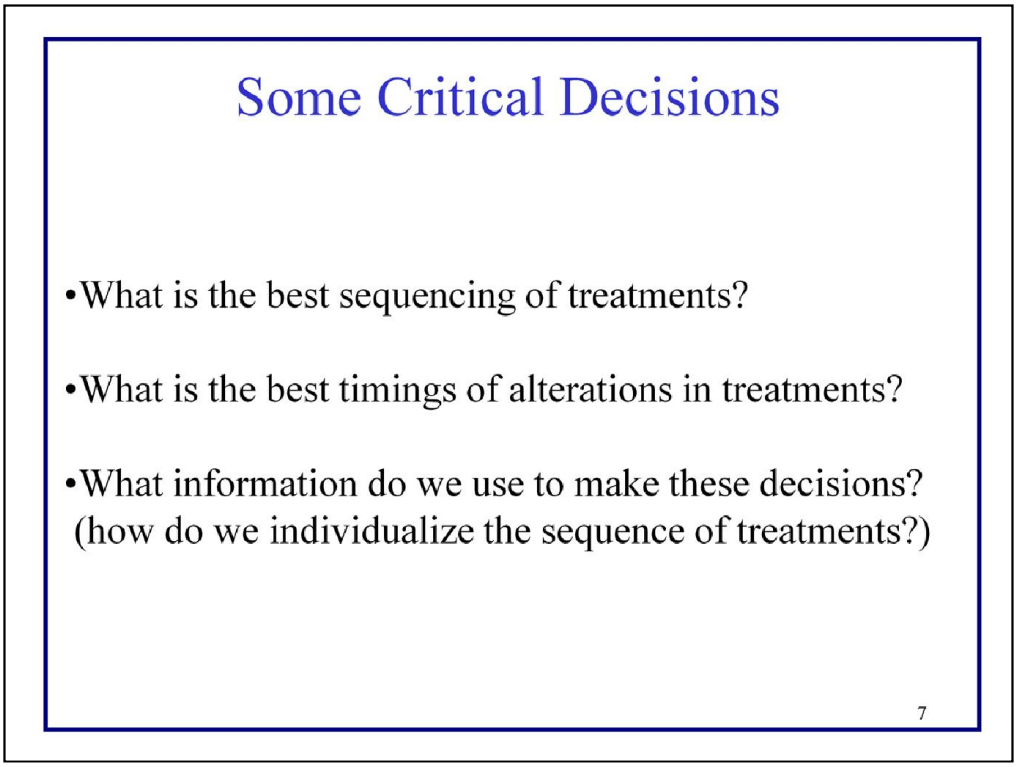


All movement between steps or stages is operationalized.
High risk: ASPD or history of formal drug abuse treatment otherwise low risk

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



This is related to clinical management of chronic disorders.

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

Outline

- Adaptive Interventions
- SMART Designs
- Trial Design Principles and Analysis
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SMART Studies

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

These are multi-stage clinical trials; each participant proceeds through stages of treatment.

Each stage begins with a critical decision and a randomization to treatment takes place at each critical decision.

Goal of trial is to inform the construction of an adaptive intervention.

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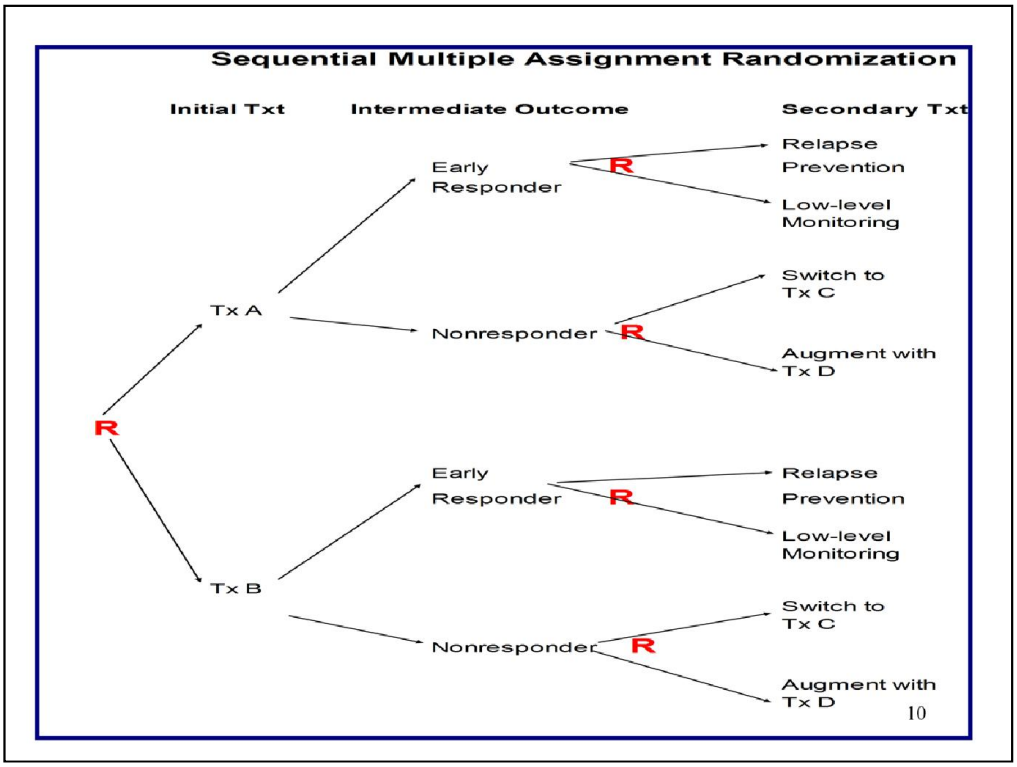
In statistics people may call these multistage trials (the randomization at each stage is assumed) or sequentially randomized trials



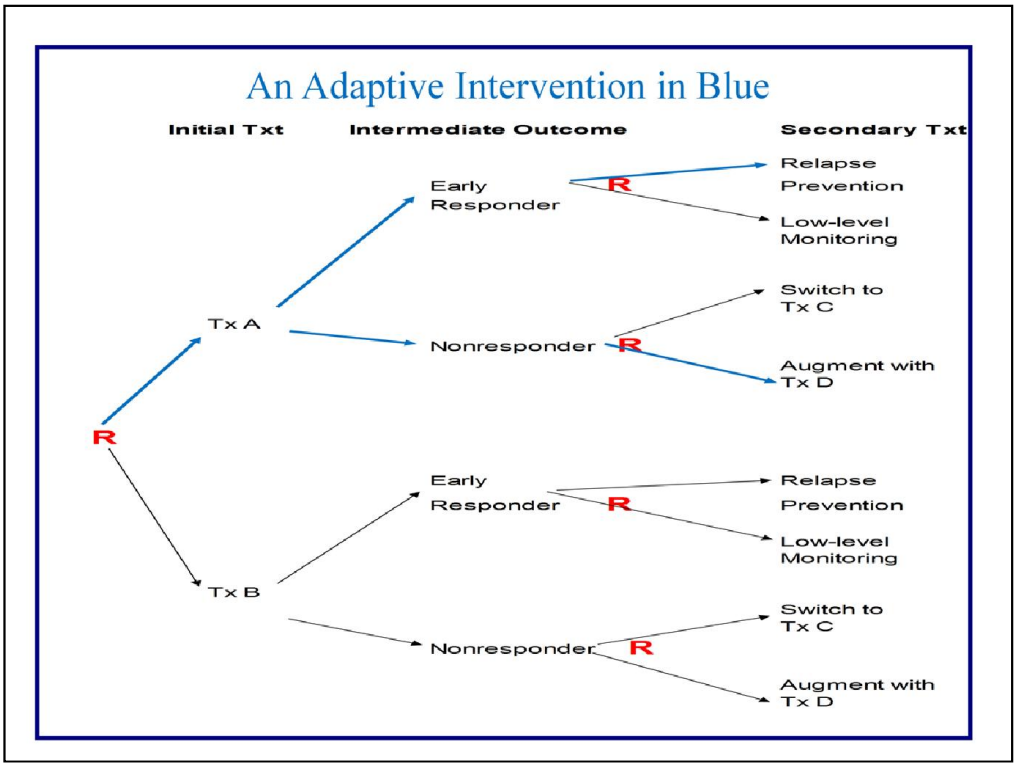
Hypothetical trial: Outcome is not shown but is on far right. The second randomization can take place up front (if you do not want to stratify or block by stage 1 outcomes such as adherence).

Equal randomization

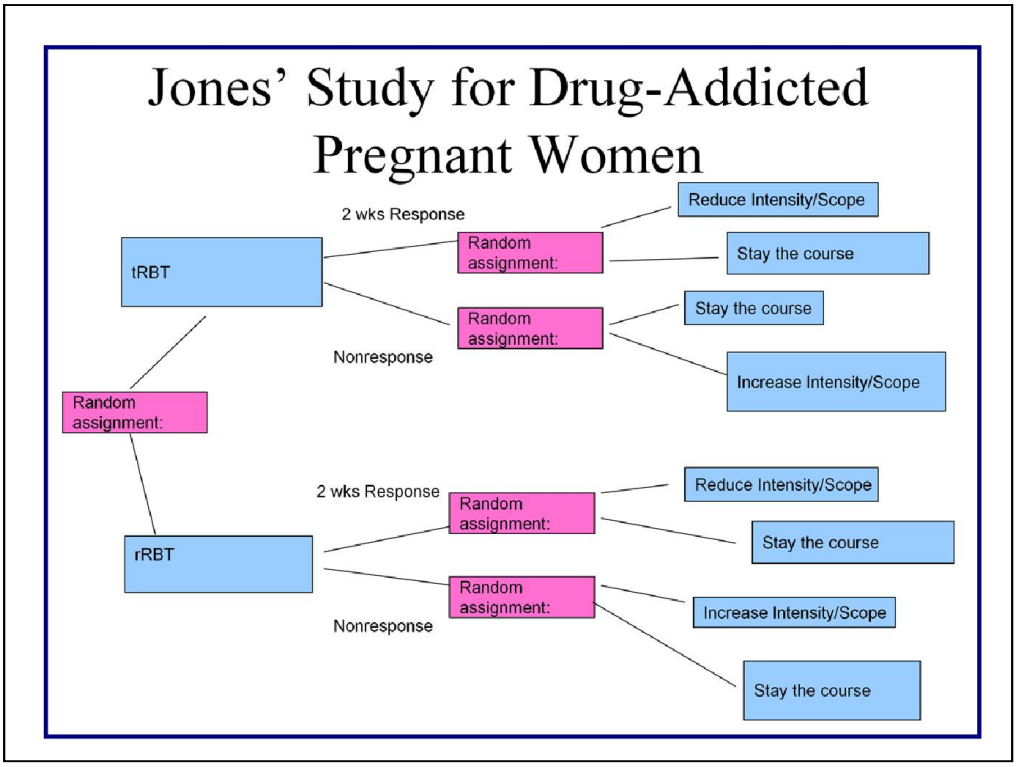
Usual reaction is (1) I'm worried about sample size and

(2) This looks awfully complicated.

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



An adaptive intervention is indicated in blue



This study is in the field n=300 primary hypothesis compared always traditional RBT vs always reduce RBT

Primary outcome is "in treatment when child born"

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

RBT==reinforcement based tx

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

aRBT is abbreviated RBT

rRBT is reduced RBT

tRBT is traditional

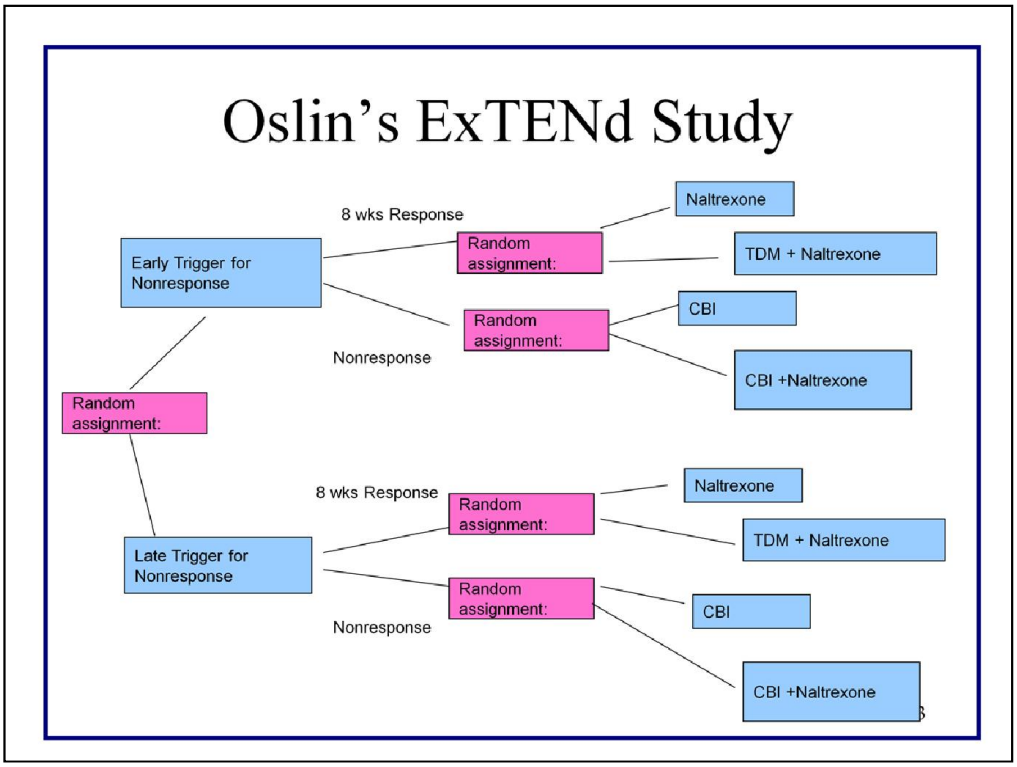
eRBT is enhanced

This trial is designed to provide data regarding how the intensity and scope of reinforcement based treatment (RBT) might be adapted to

a pregnant woman's progress in treatment. Components of RBT are:

1. Functional assessment of drug/alcohol

use
2. Use of behavioral contracts
3. Motivational interviewing style of
therapy
4. Graphing and monitoring of critical identified
behaviors to sustain abstinence
5. Abstinent-contingent access to elements
8–11 below as well as other tangible
reinforcers
6. Outreach upon first noncompliant event
7. Individual therapy
8. Recreation paid for by the program
9. Job club
10. Social club including free lunch
11. Skills-building modules



Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist then in ensuing two months are monitored for heavy drinking

Trigger for nonresponse is heavy drinking days

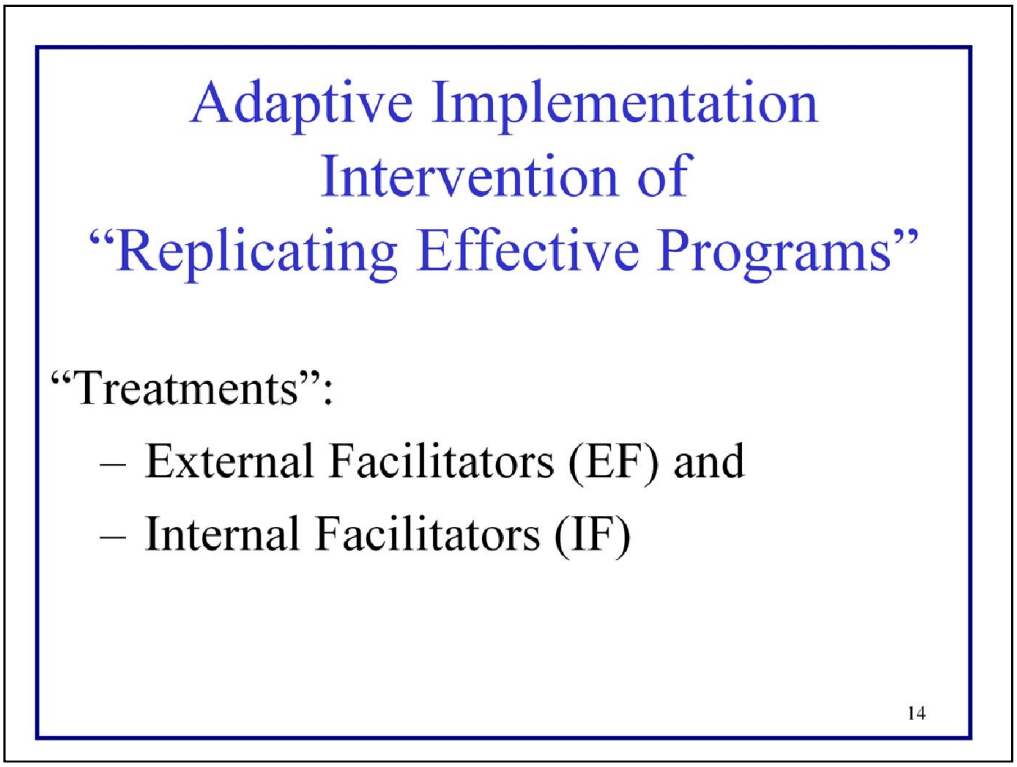
Early trigger 2 or more hdd

Late trigger 5 or more hdd

N=302

See H. Lei, I. Nahum-Shani, K. Lynch, D. Oslin and S.A. Murphy (2012). A SMART Design for Building Individualized Treatment Sequences, *The Annual Review of Clinical Psychology, Review in Advance first posted online on December 12, 2011* Vol. 8: 21-48.

for a description of this study



Replicating Effective Programs (REP) is an implementation intervention to promote use of psychosocial txt in community-based settings (site)

But, 50-75% of sites do not respond to REP alone

There are two types of REP augmentation options

> External Facilitators (EF, less expensive): Reside outside of the site, provide technical expertise by phone
>
> Internal Facilitators (IF, more expensive): Employed by sites, direct relationship to site leaders, protected time specifically for improving EBP adoption

Some sites need augmented REP, but not all sites require REP+EF+IF; Cannot do IF without EF

REP was used successfully in previous literature to help HIV/AIDS community-based settings/clinics adopt behavioral interventions for prevention and treatment.

EBP for mood disorders is Life Goals CC

Despite availability of EBPs, quality of life and outcomes for persons with mental disorders remain suboptimal because of organizational barriers.

Challenges to community-based settings include

Lack tools to embed EBPs into routine clinical care

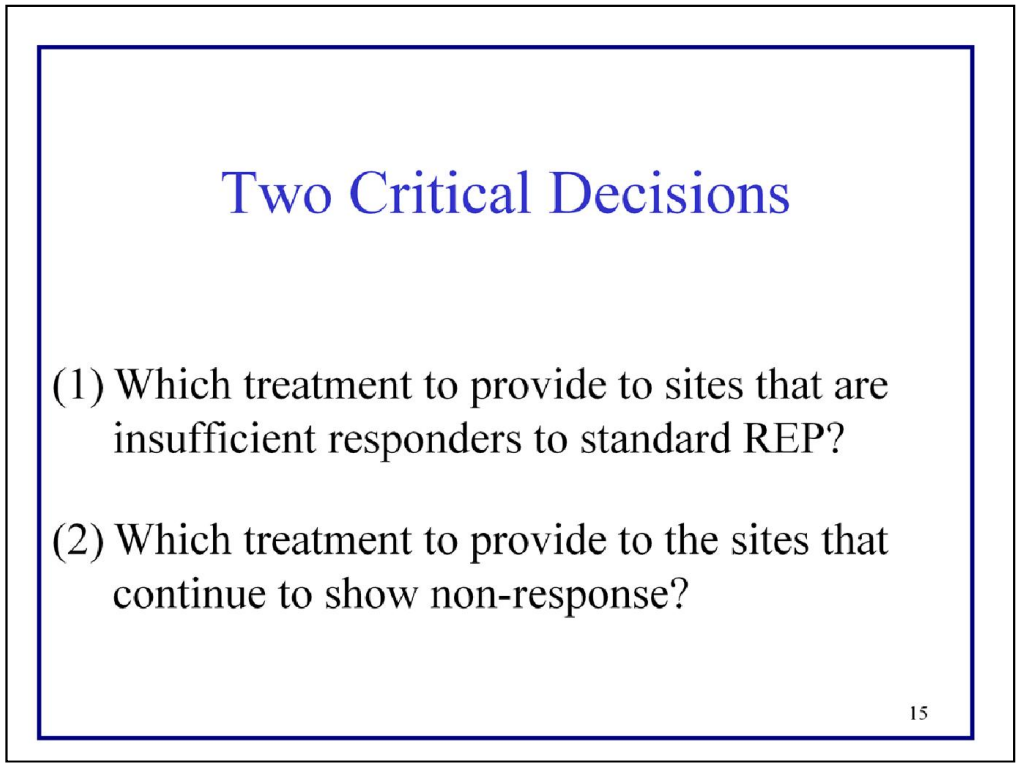
Lack of provider training, on-going support

Lack of awareness of EBPs among leaders

Providers face competing demands

In a previous preliminary study comparing REP vs REP+IF+EF, the augmented REP did much better. However, not all sites may need the IF and it is costly.

Therefore, an <u>adaptive implementation intervention</u> approach is necessary, whereby the implementation intervention may need to be augmented if sites are not responding (i.e., not adopting EBPs) to REP alone. In contrast to measuring correlates of implementation non-response, <u>adaptive implementation interventions are augmented, or stepped, in direct response to limited uptake of EBPs among specific sites based on circumstances that may not be observable at baseline</u>.



Primary Aim: To examine, among sites that do not respond to **REP** at month 6, the effect of **REP+EF+IF** versus **REP+EF** on changes (6mo to 18mo) in MH-QOL (primary), # LG encounters, psych sx, functionality, cost-effectiveness ($/QOL) (secondary).

Aim 2: To determine, among **REP+EF** sites with continued non-response after 12 months, the effect of continued **REP+EF** vs. **REP+EF+IF** on outcomes at 24 months.

Implementation of EBPs in Mental Health

Takes years to translate evidence-based practices (EBPs) into community-based settings (clinic sites)

An example

Life Goals Collaborative Care

•This is the EBP intervention they are trying to get community based practices to take up

•An evidence-based psychosocial treatment shown to improve outcomes among patients with mood disorders (depression and bipolar) in 6 RCTs across mental health and primary care settings.

- •Outcomes include: 3 point decrease in PHQ-9 scores, 9 fold increase in prob of depression remission; 4 point increase in physical and mental health quality of life

•Effective in patients with co-occurring substance use disorders

•Based on social cognitive theory

•Delivered in 4 two-hour weekly group sessions (see below) + at least 6 individualized care management contacts

    •Contacts are designed to encourage active discussions focused on individuals' personal goals that are aligned with healthy behavior change

More details on Life Goals Components Group Sessions

Four sessions lasting 60-80 minutes focused on active discussions around personal goals, psychiatric symptoms, stigma, and health behaviors

Session 1: Personal goals

Personal goals and self-management; Understanding stigma; Symptoms & wellness

Session 2: Depressive symptoms (sx)

Overview, triggers to depressive episodes; Action plan for depression, self-assessment

Session 3: Anxiety/manic sx

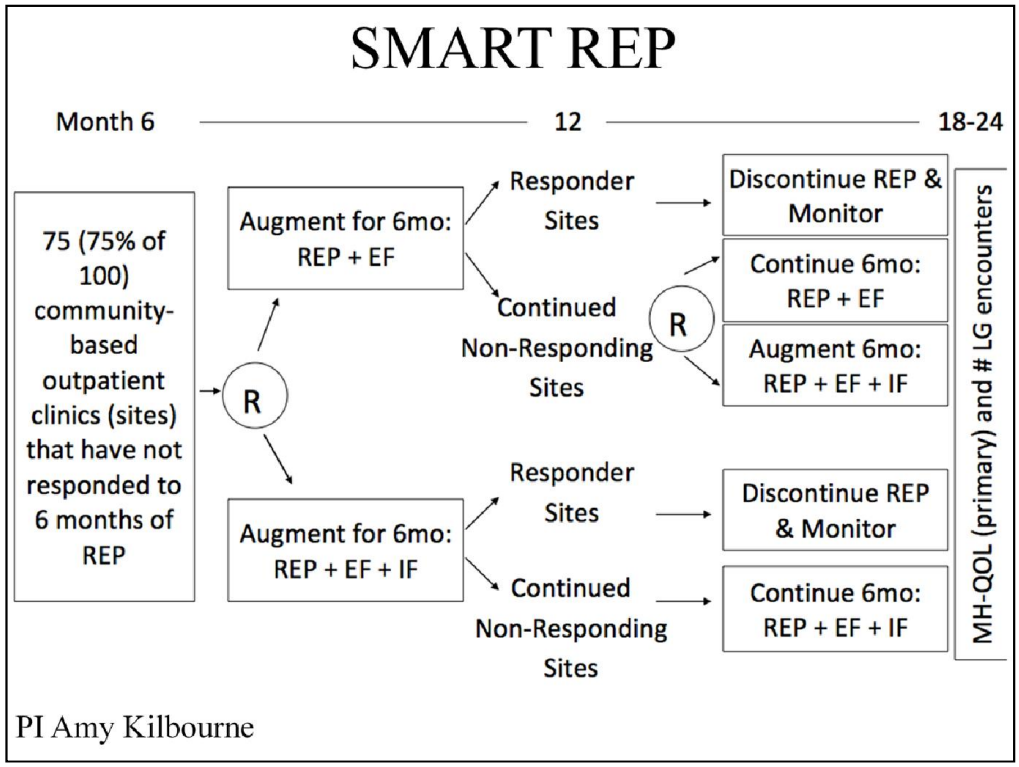
Overview, triggers to episodes; Action plan: anxiety/mania, self-assessment

Session 4: Wellness plan

Building behavior change goals; Relapse prevention and monitoring, medications

More details on Life Goals Individualized sessions

Provider makes 6 regular individual contacts (15-20 min), encouraging ongoing healthy behavior change tied to symptom coping strategies, addressing barriers to behavior change, and encouraging ongoing symptom and behavior monitoring



The unit of randomization (i.e., the unit of intervention) is the clinic/site. Approximately 100 clinics in total from Colorado, Michigan and Arkansas.

The unit of outcome/analysis is the patient. Approximately1500 patients in total (~20 patients per clinic are expected to be identified). These patients are all identified a priori (i.e., at Month 0, prior to REP) as having a mood disorder and needing Life Goals intervention.

The embedded tailoring variable (response/non-response) is defined at 6 and 12 months in terms of both treatment (Life Goals intervention) uptake and treatment engagement/adherence.

It is defined as having ≥50% patients enrolled in LG with ≥75% sessions completed.

The primary outcome is longitudinal mental health quality of life (MH-QOL).

The primary contrast is the comparison of REP+IF+EF vs REP+EF at month 6 on (change in) outcomes **at month 18**.

Secondary outcomes include: # Life Goals encounters (recall max is 10 for each patient), psychiatric symptoms, functional impairment, and cost-effectiveness.

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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 (adherence, etc.); information that might be used to individualize subsequent treatment.

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Note we considered different txt's for the responders as compared to the nonresponders.

In mental illness studies feasibility considerations may force us to use preference in this low dimensional summary.

SMART Design Principles

•Choose primary hypotheses that are both scientifically important and aid in developing the adaptive intervention.

- •Power trial to address these hypotheses.

•Conduct secondary analyses that further develop the adaptive intervention (take advantage of the randomization in eliminating confounding).

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SMART Designing Principles: Primary Hypothesis

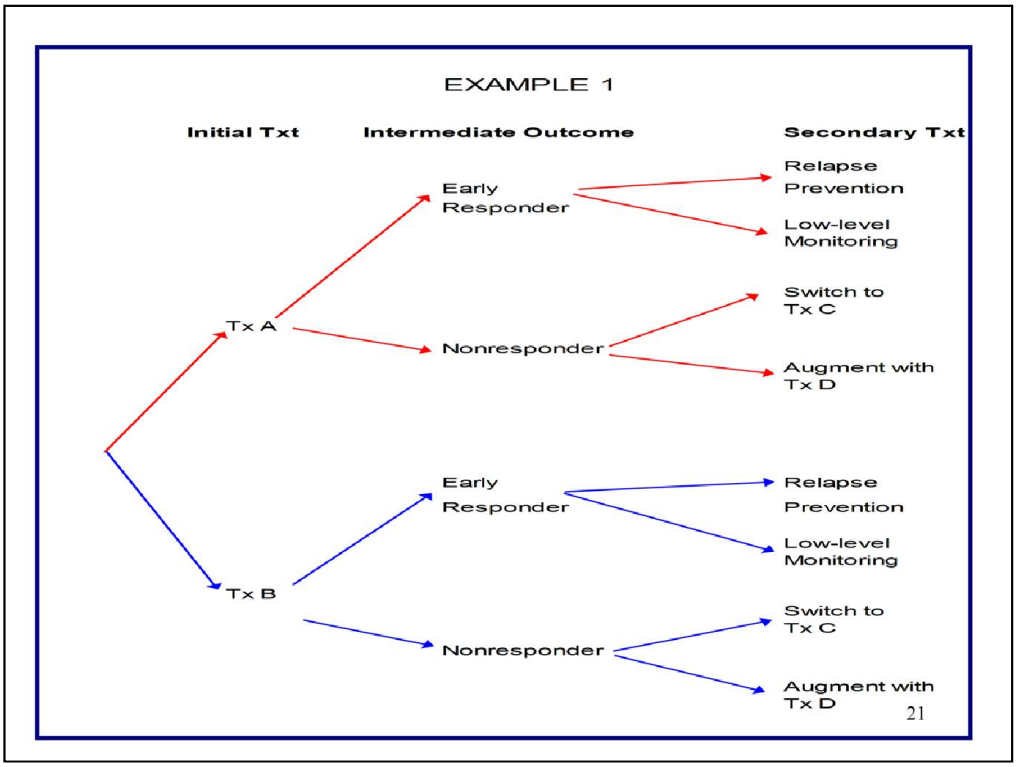
•EXAMPLE 1: (*sample size is highly constrained*): Hypothesize that adaptive interventions beginning with treatment A result in lower symptoms than adaptive interventions beginning with treatment B.

•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

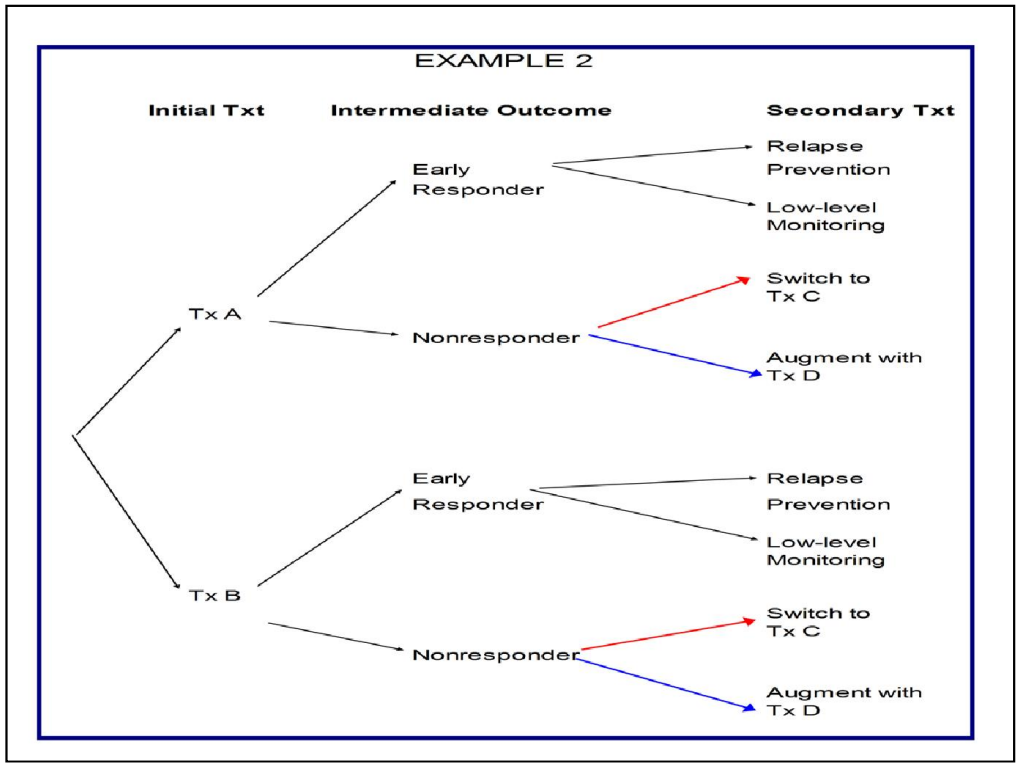
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

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

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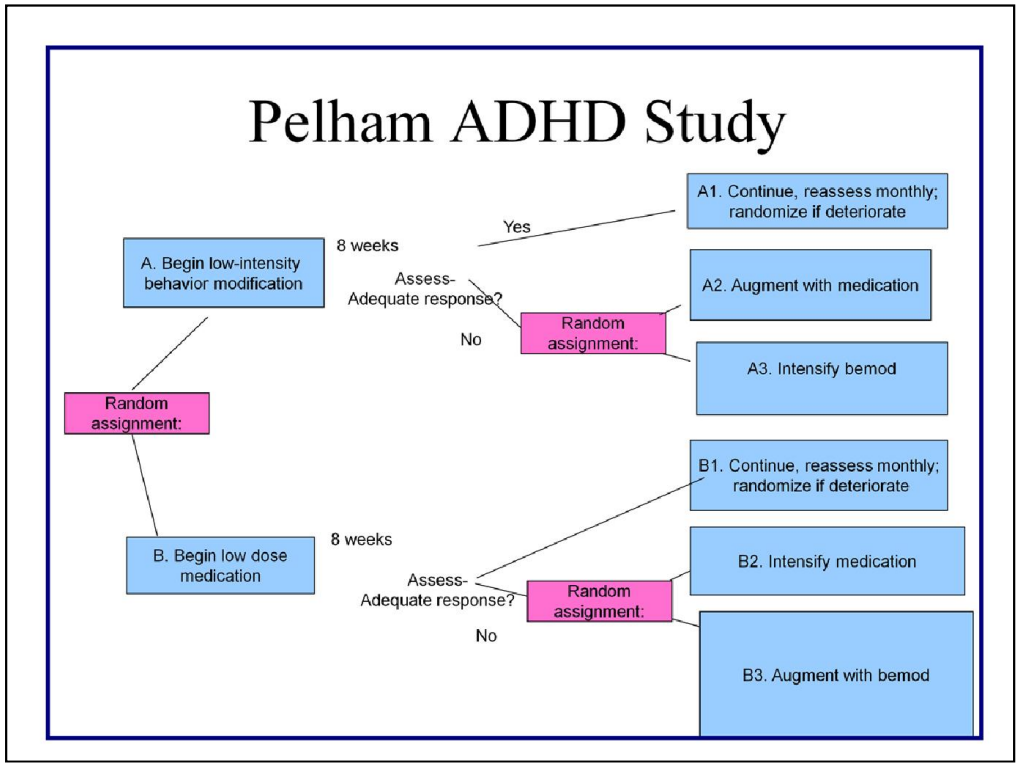

The medication is Ritalin

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.

Our outcome will be a teacher rated classroom performance recorded at 8 months. N=149

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. Psychological Methods 17(4), 457-477.

II. I. Nahum-Shani, M. Qian, D. Almiral, W.. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2012). Q-Learning: A Data Analysis Method for Constructing Adaptive Interventions. Psychological Methods 17(4):478-94.

Exploring Greater Individualization via Q-Learning

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

- This regression results in a proposal for an optimal adaptive intervention.
- A subsequent trial would evaluate the proposed adaptive intervention.

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Q-Learning using data on children with ADHD

- Stage 1 data: (X_1, A_1, R_1)
  - $R_1=1$ if responder; $=0$ if non-responder
  - $A_1=1$ if BMOD, $A_1=-1$ if MED
- X_1 includes baseline school performance, Y_0, whether medicated in prior year (S_1), ODD (O_1)
  - $S_1=1$ if medicated in prior year; $=0$, otherwise.
- Stage 1 involves all children

28

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -1 if augment

Q-Learning using data on children with ADHD

- Stage 2 data: (X_2, A_2, Y)
  - Y = end of year school performance
  - $A_2=1$ if Intensify, $A_2=-1$ if Augment
  - X_2 includes the month of non-response, (M_2) and a measure of adherence in stage 1 (S_2)
    - $S_2=1$ if adherent in stage 1; $=0$, if non-adherent
- Stage 2 involves only children who do not respond in Stage 1 $(R_1=0)$.

29

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -1 if augment

Q-Learning for SMART Studies

- Conduct the regressions in backwards order! E.g. Stage 2 first, then Stage 1.
- Why?
  - Stage 1 dependent variable must include effects of Stage 2 treatment.
  - Stage 1 dependent variable is a predictor of Y under optimal treatment in stage 2.
  - Stage 2 analysis is used to construct the stage 1 dependent variable—the predictor of Y, $\hat{Y}$

30

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -1 if augment

Stage 2 Regression for Non-responding Children

- Dependent Variable: Y (end of school year performance)
- Treatment: $A_2=1$ if Intensify, $A_2=-1$ if Augment
- Interactions with Treatment, A_2: stage 1 treatment (A_1) and adherence (S_2)
- Controls: baseline school performance, (Y_0) and baseline prior medication (S_1), month of non-response (M_2)

31

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -1 if augment

Q-Learning using data on children with ADHD

- Stage 2 regression for Y:

$$\alpha_{21} + \alpha_{22}Y_0 + \alpha_{23}S_1 + \alpha_{24}O_1 + \alpha_{25}A_1 + \alpha_{26}M_2 + \alpha_{27}S_2 + (\beta_{21} + \beta_{22}A_1 + \beta_{23}S_2)A_2$$

- **Interesting Stage 2 contrast**: Does the best stage 2 tactic (intensify versus augment) differ by whether the child/family is adherent?

32

A1=1 if BMOD, -1 if MED

S2=1 if adherent to initial txt; S2=0 if nonadherent to initial treatment.

A2=1 if intensify, -1 if augment

Q-Learning using data on children with ADHD

- Decision rule is "if child is non-responding then intensify initial treatment if $-.72 + .05A_1 + .97S_2 > 0$, otherwise augment"

Decision Rule for Non-responding Children	Initial Treatment =BMOD	Initial Treatment=MED
Adherent	Intensify	Intensify
Not Adherent	Augment	Augment

33

A1=1 if BMOD, -1 if MED

S2=1 if adherent to initial txt.

A2=1 if intensify, -1 if augment

Stage 1 Regression for All Children

- Dependent Variable: $\hat{Y}$ (predicted end of school year performance under optimal stage 2 treatment)
- Treatment: A_1=*1* if BEMOD, A_1=*-1* if MED
- Interactions with Treatment, A_1: prior medication (S_1)
- Control: baseline school performance, (Y_0), baseline ODD, (O_1)

34

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

S1= 1 if prior meds, 0 otherwise

Constructing the Dependent Variable for the Stage 1 Regression

- Stage 2 regression for Y:

$$\alpha_{21} + \alpha_{22}Y_0 + \alpha_{23}S_1 + \alpha_{24}O_1 + \alpha_{25}A_1 + \alpha_{26}M_2 + \alpha_{27}S_2 + (\beta_{21} + \beta_{22}A_1 + \beta_{23}S_2)A_2$$

- Stage 1 dependent variable:

$$R_1 Y + (1 - R_1)\hat{Y}$$

$$\hat{Y} = \hat{\alpha}_{21} + \hat{\alpha}_{22}Y_0 + \hat{\alpha}_{23}S_1 + \hat{\alpha}_{24}O_1 + \hat{\alpha}_{25}A_1 + \hat{\alpha}_{26}M_2 + \hat{\alpha}_{27}S_2 + |\hat{\beta}_{21} + \hat{\beta}_{22}A_1 + \hat{\beta}_{23}S_2|$$

Q-Learning using data on children with ADHD

- Stage 1 regression for $\widehat{Y}$:

$$\alpha_{11} + \alpha_{12}Y_0 + \alpha_{13}S_1 + \alpha_{14}O_1 + (\beta_{11} + \beta_{12}S_1)A_1$$

- **Interesting Stage 1 contrast**: does the best initial treatment differ by whether a child received medication in the prior year for ADHD?

36

S1=1 if on med in prior year, =0 otherwise

Q-Learning using data on children with ADHD

- Decision rule is "Begin with BMOD if $.17 - .32S_1 > 0$, otherwise begin with MED"

Initial Decision Rule	Initial Treatment
Prior MEDS	MEDS
No Prior MEDS	BMOD

37

S1= 1 if prior meds, =0 if not.

A1=1 if BMOD, -1 if MED

1st Adaptive Intervention Proposal

IF medication was not used in the prior year
THEN begin with BMOD;
ELSE select MED.

IF the child is nonresponsive and was non-adherent, THEN augment present treatment;
ELSE IF the child is nonresponsive and was adherent, THEN intensify current treatment.

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ADHD Example

- The adaptive intervention is quite decisive. We developed this adaptive intervention using a trial on *only 138 children*. Is there sufficient evidence in the data to warrant this level of decisiveness??????
- Would a similar trial obtain similar results?
- There are strong opinions regarding how to treat ADHD.
- One solution –use confidence intervals.

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ADHD Example

Treatment Decision for Non-responders. Positive Treatment Effect → Intensify

	90% Confidence Interval
Adherent to BMOD	(-0.08, 0.69)
Adherent to MED	(-0.18, 0.62)
Non-adherent to BMOD	(-1.10, -0.28)
Non-adherent to MED	(-1.25, -0.29)

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ADHD Example

Initial Treatment Decision: Positive Treatment Effect → BMOD

	90% Confidence Interval
Prior MEDS	(-0.48, 0.16)
No Prior MEDS	(-0.05, 0.39)

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2nd Adaptive Intervention Proposal

IF medication was not used in the prior year
THEN begin with BMOD;
ELSE select either BMOD or MED.

IF the child is nonresponsive and was non-adherent, THEN augment present treatment;
ELSE IF the child is nonresponsive and was adherent, THEN select either intensification or augmentation of current treatment.

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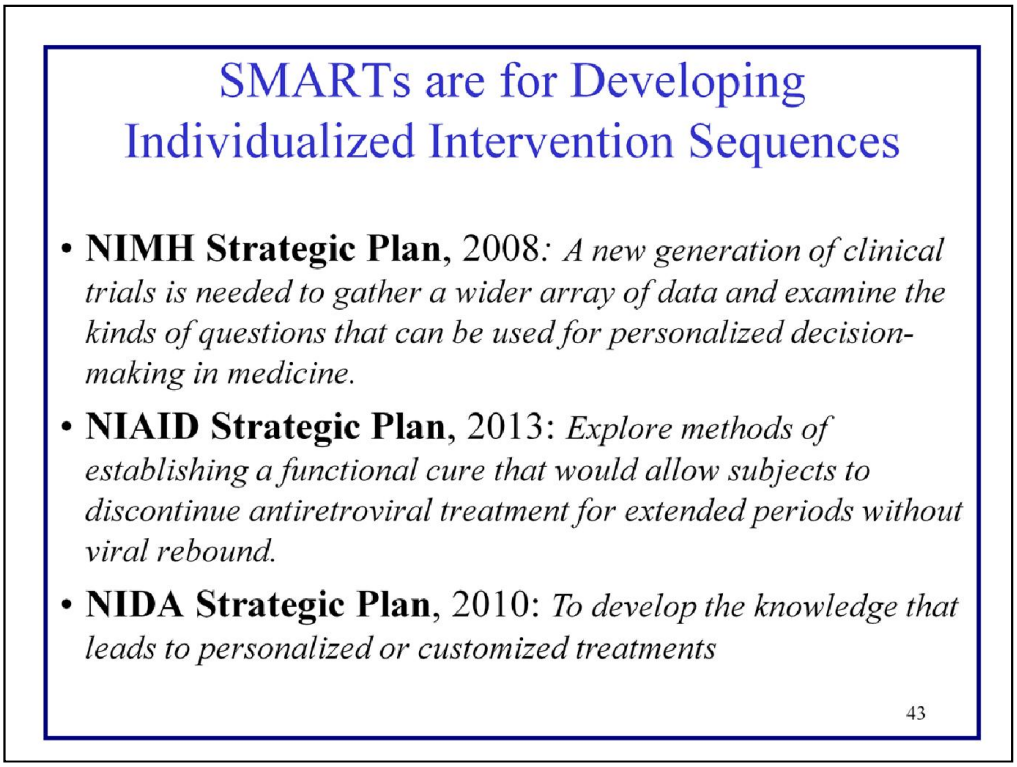

NIMH Strategic Plan, 2008: Support research that tailors psychosocial and biomedical interventions to different kinds of providers (e.g., psychologists, psychiatrists, psychiatric nurses, social workers) and different intervention settings (e.g., schools, mental health clinics, community health clinics).

personalized medicine: tailoring pharmacological, behavioral, and other forms of treatment to the needs of each individual. A new generation of clinical trials is needed to gather a wider array of data and examine the kinds of questions that can be used for personalized decision-making in medicine.

Discussion

- For Q-Learning Software in R and in SAS:

http://methodology.psu.edu/downloads

- For examples of SMARTs, see:

http://methodology.psu.edu/ra/adap-treat-strat/projects

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Where are we going?.....

- Increasing use of wearable computers (e.g smart phones, etc.) to both collect real time data and provide just-in-time adaptive interventions.

- We are working on the design of studies aimed at constructing and optimizing just-in-time adaptive interventions.

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This seminar can be found at:

http://www.stat.lsa.umich.edu/~samurphy/seminars/northwestern.1.27.14.pdf

This seminar is based on work with many collaborators, some of which are: L. Collins, E. Laber, M. Qian, D. Almirall, K. Lynch, J. McKay, C. Kasari, H. Jones, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham. Email with questions or if you would like a copy:

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