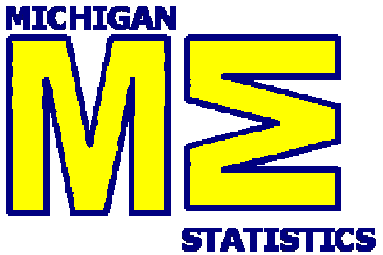
Using Data to Inform Sequential, Individualized Clinical Decision Making

S.A. Murphy



Outline

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

Adaptive Interventions are individually tailored sequences of interventions, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

- 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

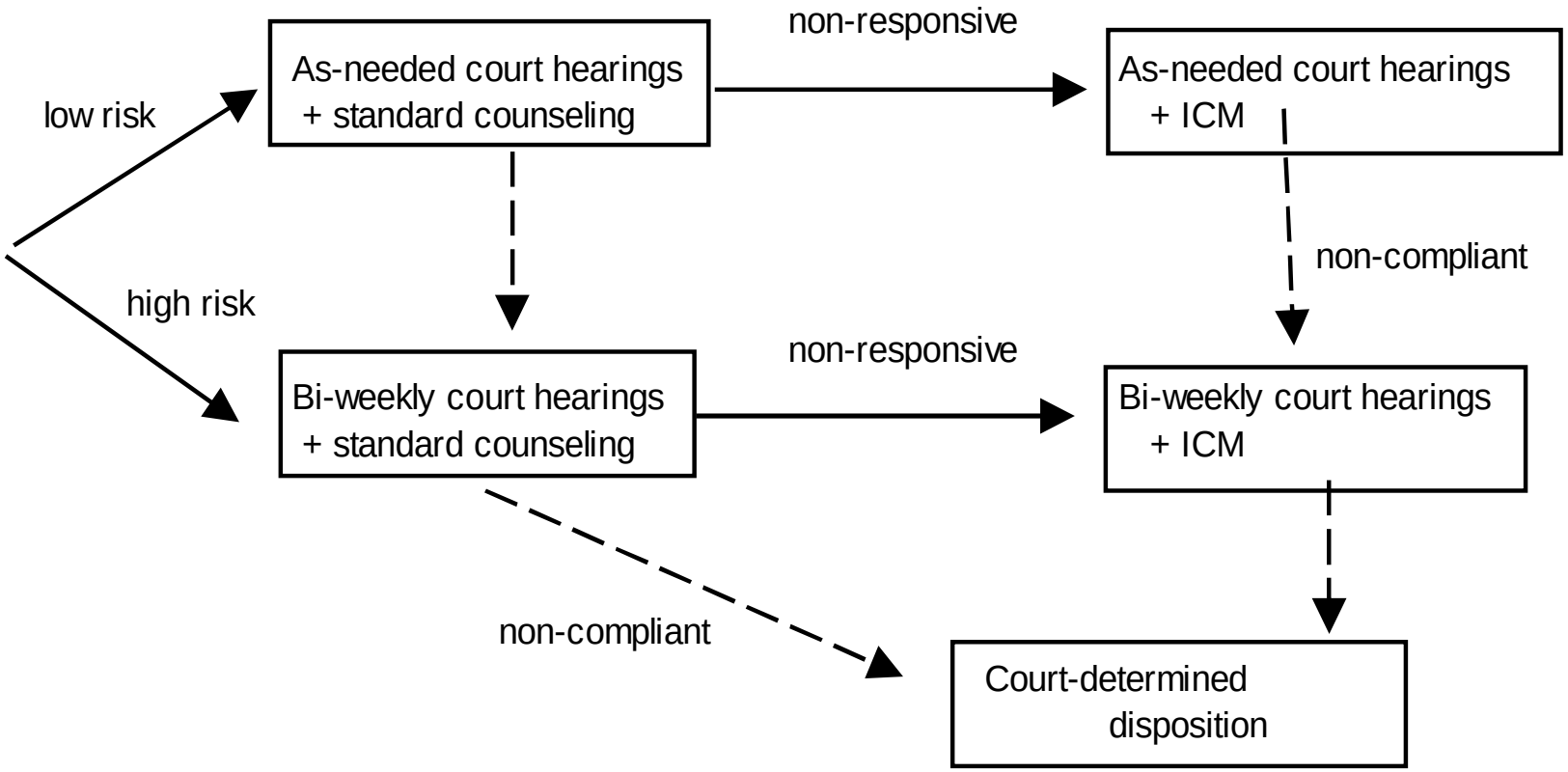
Why Adaptive Interventions?

- High heterogeneity in response to any one treatment
  - What works for one person may not work for another
  - What works now for a person may not work later (and relapse is too common)
- Lack of adherence or excessive burden is common
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient

Example of an Adaptive Intervention

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

Adaptive Drug Court Program



The Big Questions

- 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?)

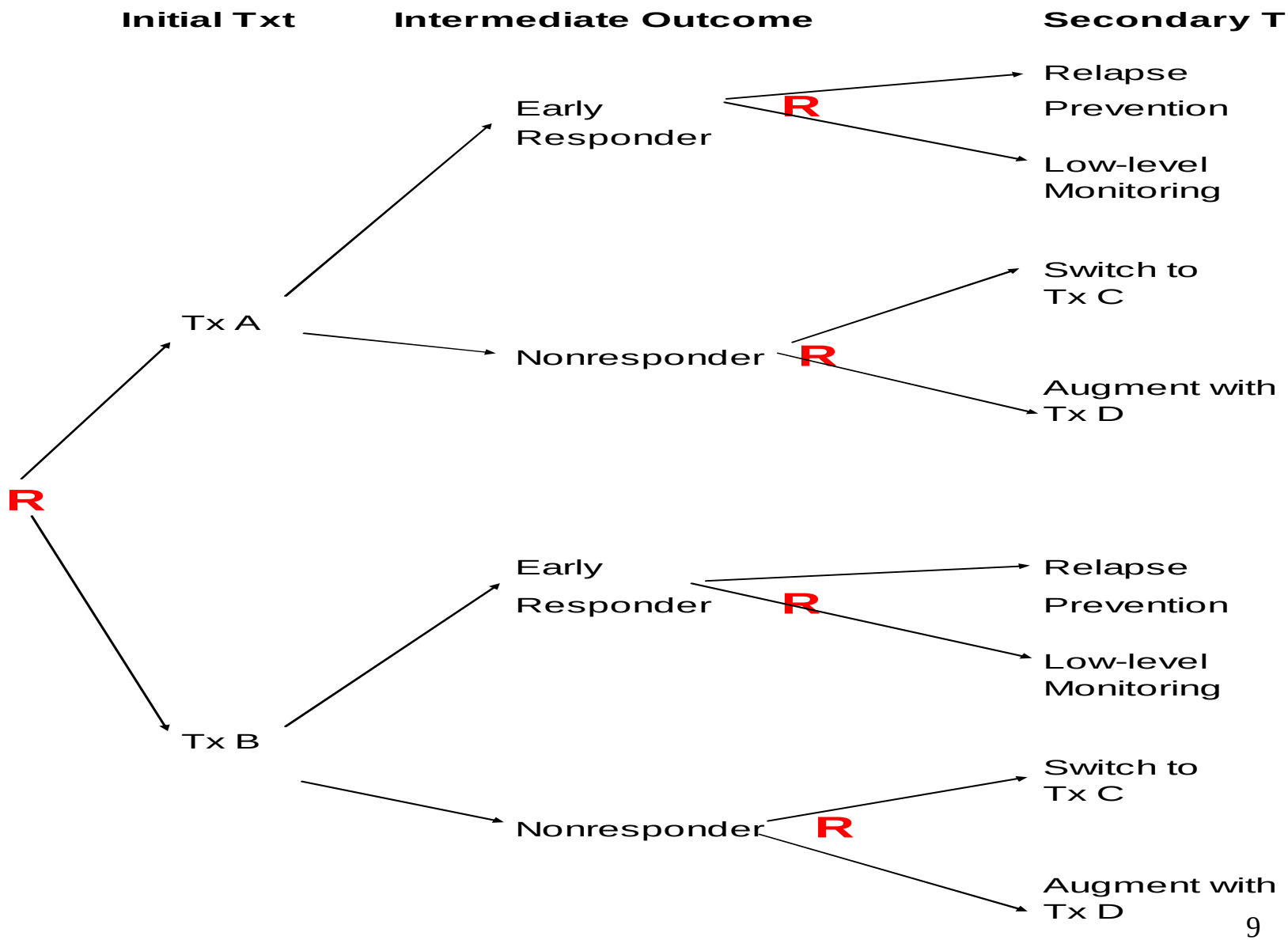
Why SMART Studies?

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 of trial is to inform the construction of adaptive interventions.

Sequential Multiple Assignment Randomization



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

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 treatment.

SMART Design Principles

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

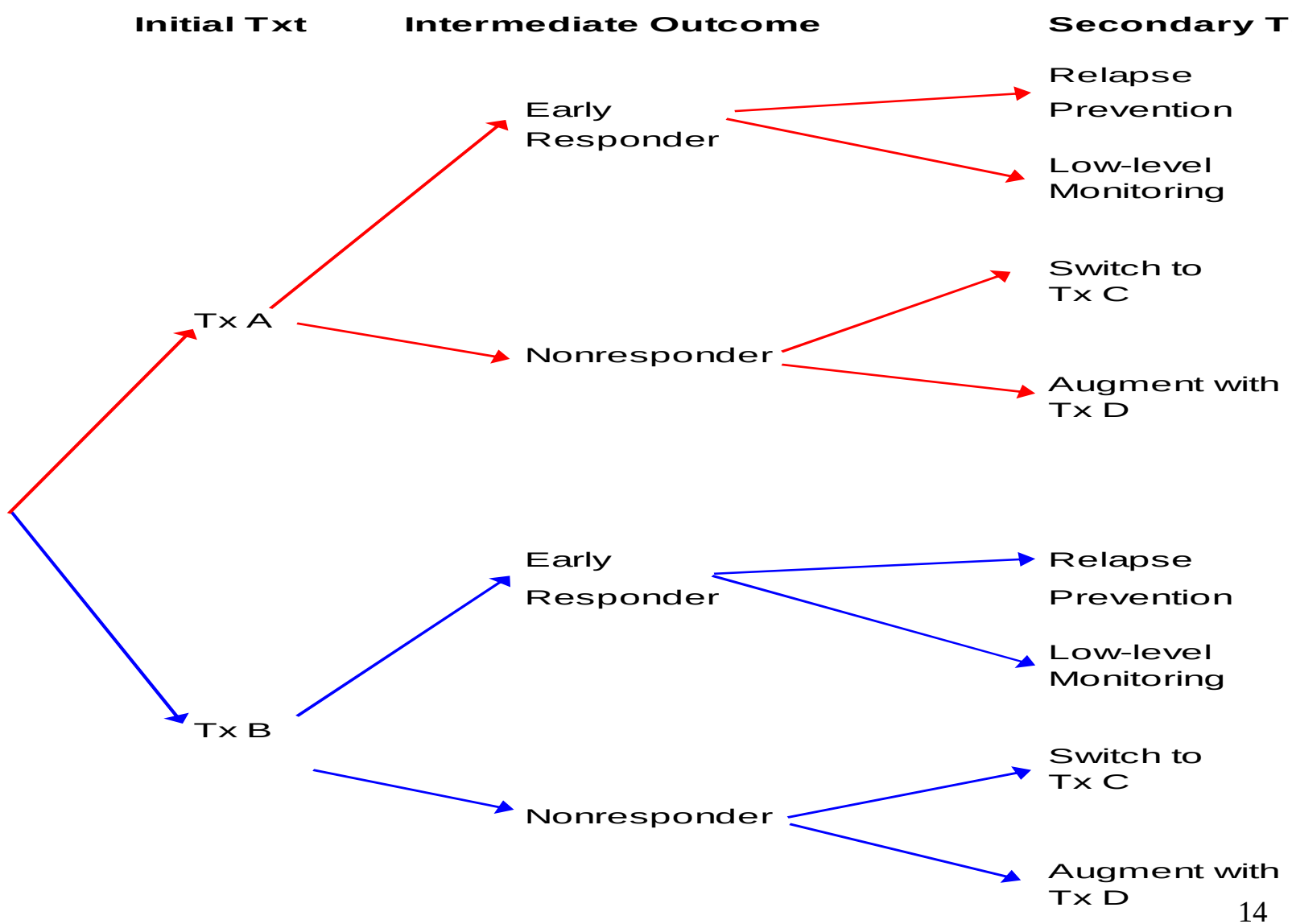
  •Power trial to address these hypotheses.

•Conduct secondary analyses that further develop the adaptive intervention and that use the randomization to eliminate confounding.

SMART Designing Principles: Primary Hypothesis

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

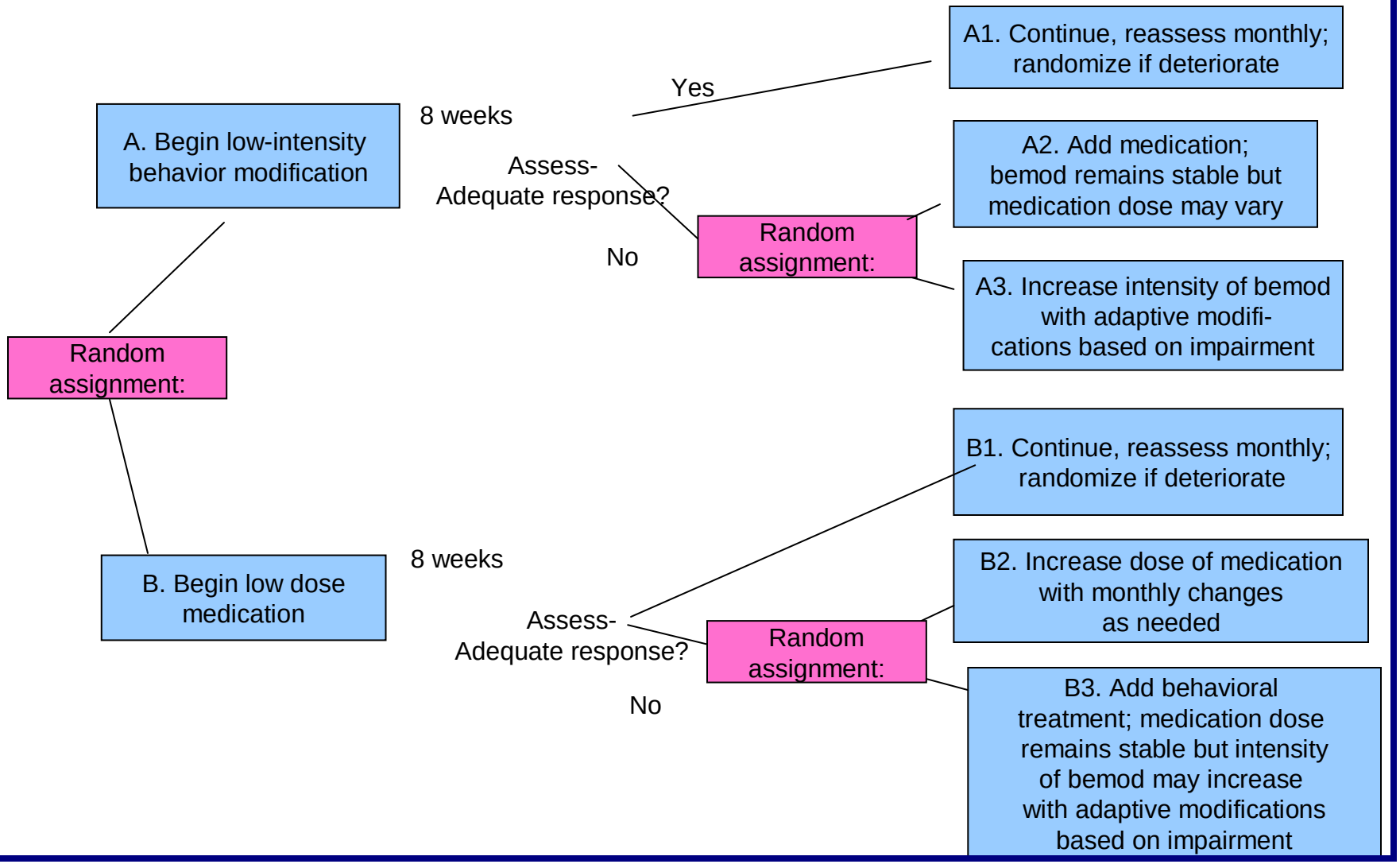
EXAMPLE 1


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

Exploring Greater Individualization using the "Adaptive Interventions for Children with ADHD" study (W. Pelham, PI)

Q-Learning

Example: Pelham ADHD Study



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.

Adaptive Interventions for 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) and prior medication (S_1)
    - $S_1 = 1$ if prior use of medication; $= 0$, if not.
- Stage 1 involves all children

Adaptive Interventions for Children with ADHD

- Stage 2 data: (X_2, A_2, Y)
  - Y = end of year school performance
  - A_2=*1* if Enhance, 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*).

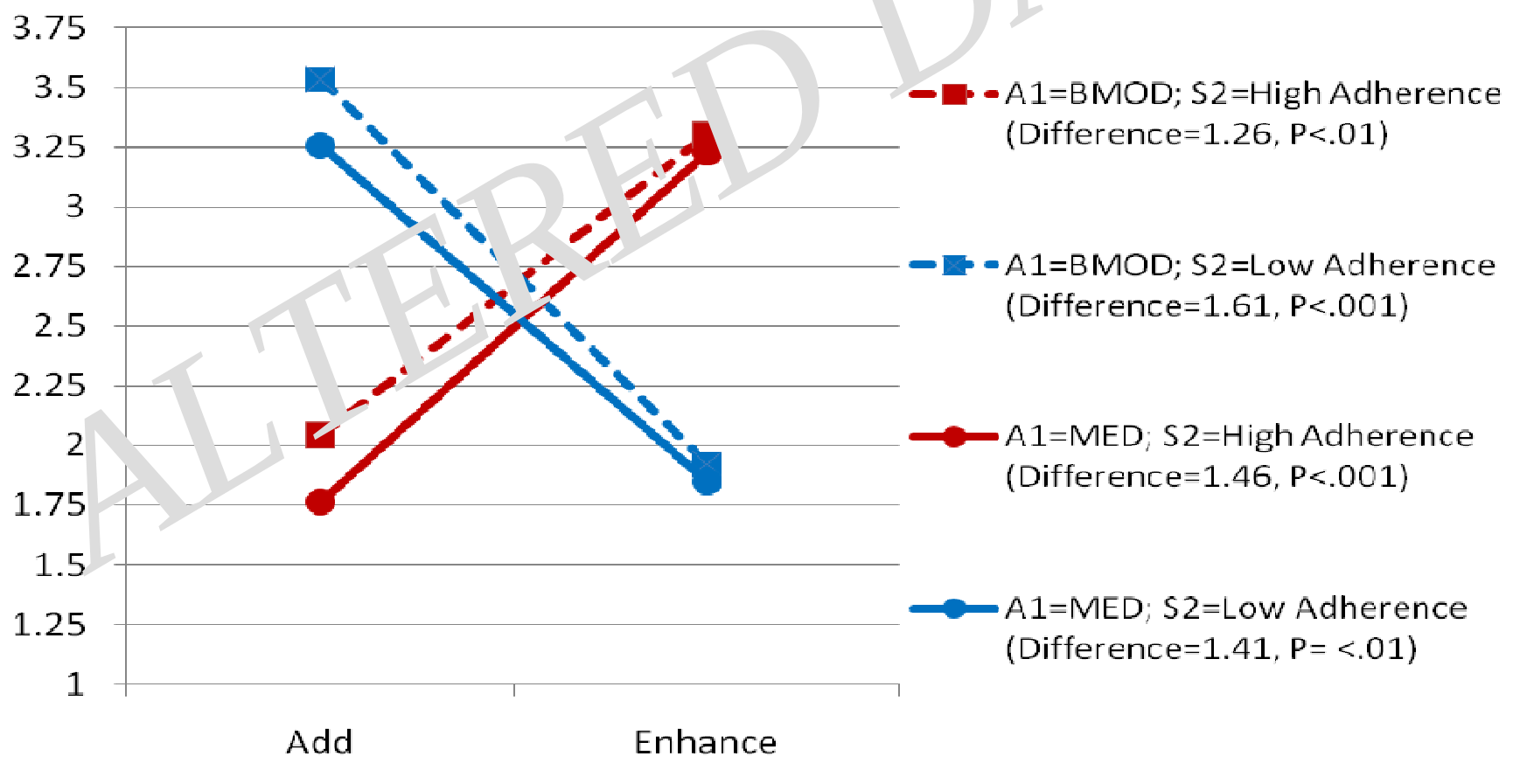
Q-Learning for SMART Studies

- Conduct the regressions in backwards order! E.g. Stage 2 first, then Stage 1.
- Why?
  - Stage 1 dependent variable must control for 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 predictor of Y, $\hat{Y}$

Stage 2 Regression for Non-responding Children

- Dependent Variable: Y (end of school year performance)
- Treatment: $A_2=1$ if Enhance, $A_2=-1$ 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)

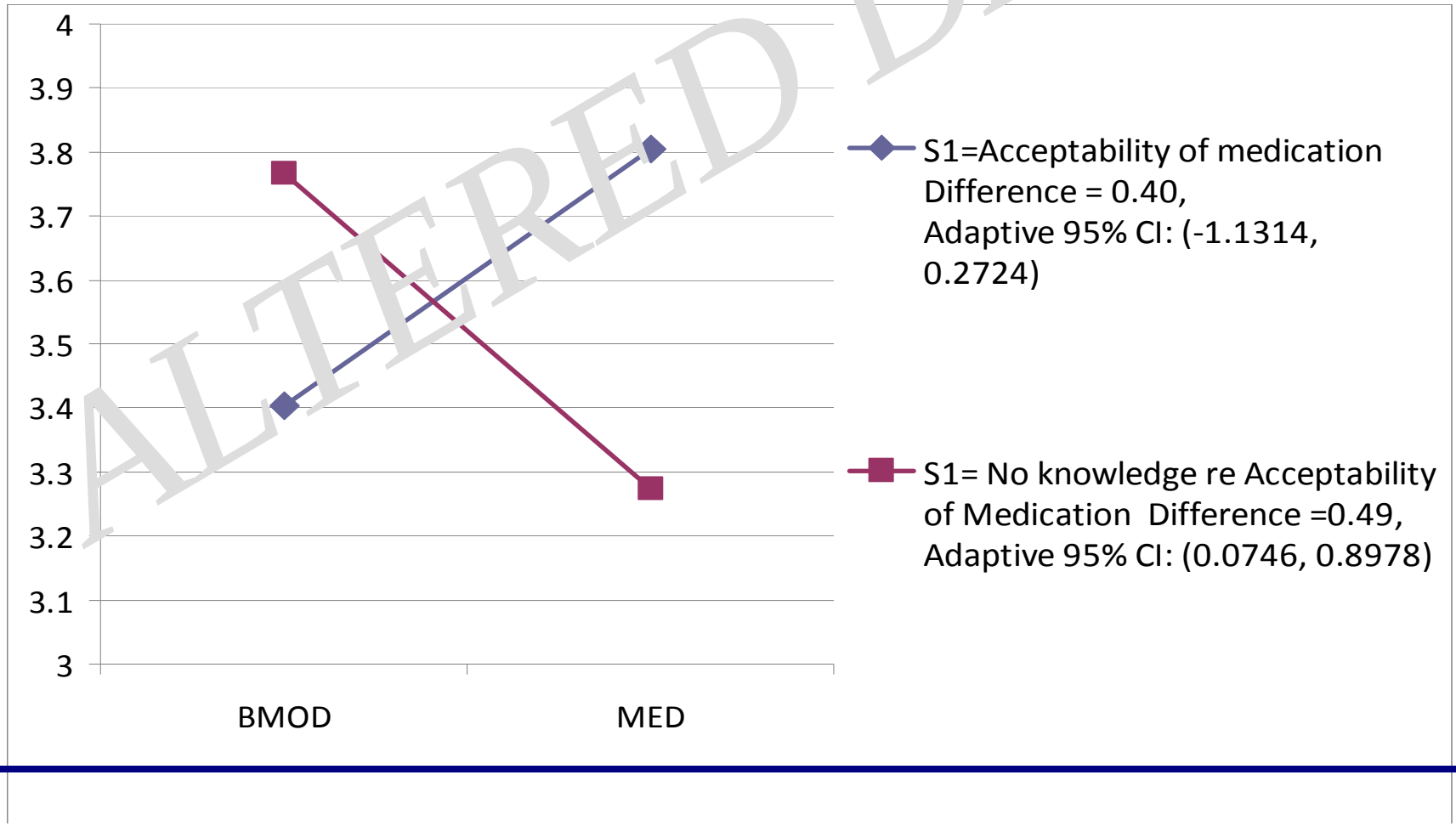
Stage 2 Regression for Non-responding Children



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)

Stage 1 Regression for All Children



Adaptive Intervention Proposal

IF medication has not been 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 nonresponse and was adherent, THEN select intensification of current treatment.

Discussion

- Software in R for Q-Learning out and, in SAS, is coming out soon!

https://methodology.psu.edu/ra/adap-treat-strat/qlearning

- Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.

This seminar can be found at:

http://www.stat.lsa.umich.edu/~samurphy/seminars/SBM.04.29.11.pdf

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

samurphy@umich.edu

Adaptive Treatments for Children with ADHD

- Stage 2 regression for Y:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_2\beta_{23})$$

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

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$

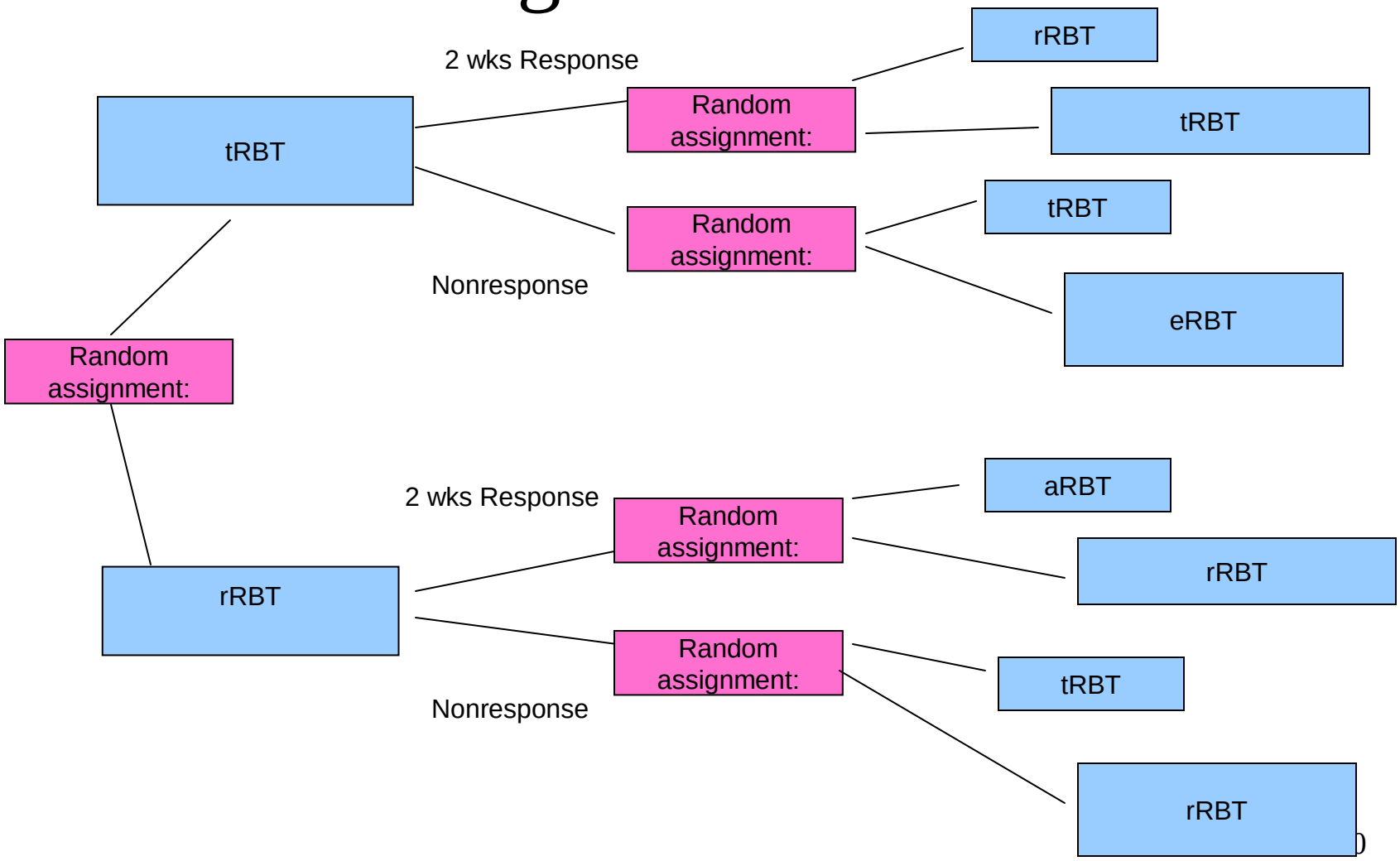
Adaptive Treatments for Children with ADHD

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

$$(1, Y_0, S_1)\alpha_1 + A_1(\beta_{11} + S_1\beta_{12})$$

- Interesting stage 1 contrast: should the knowledge that medication is highly acceptable, determine the best initial treatment in the sequence?

Jones' Study for Drug-Addicted Pregnant Women



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