SMART Study Designs for Developing Interventions

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Outline

- Adaptive Interventions
- SMART 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, 2012) Drug Court
- Rush et al. (2003) Treatment of Depression

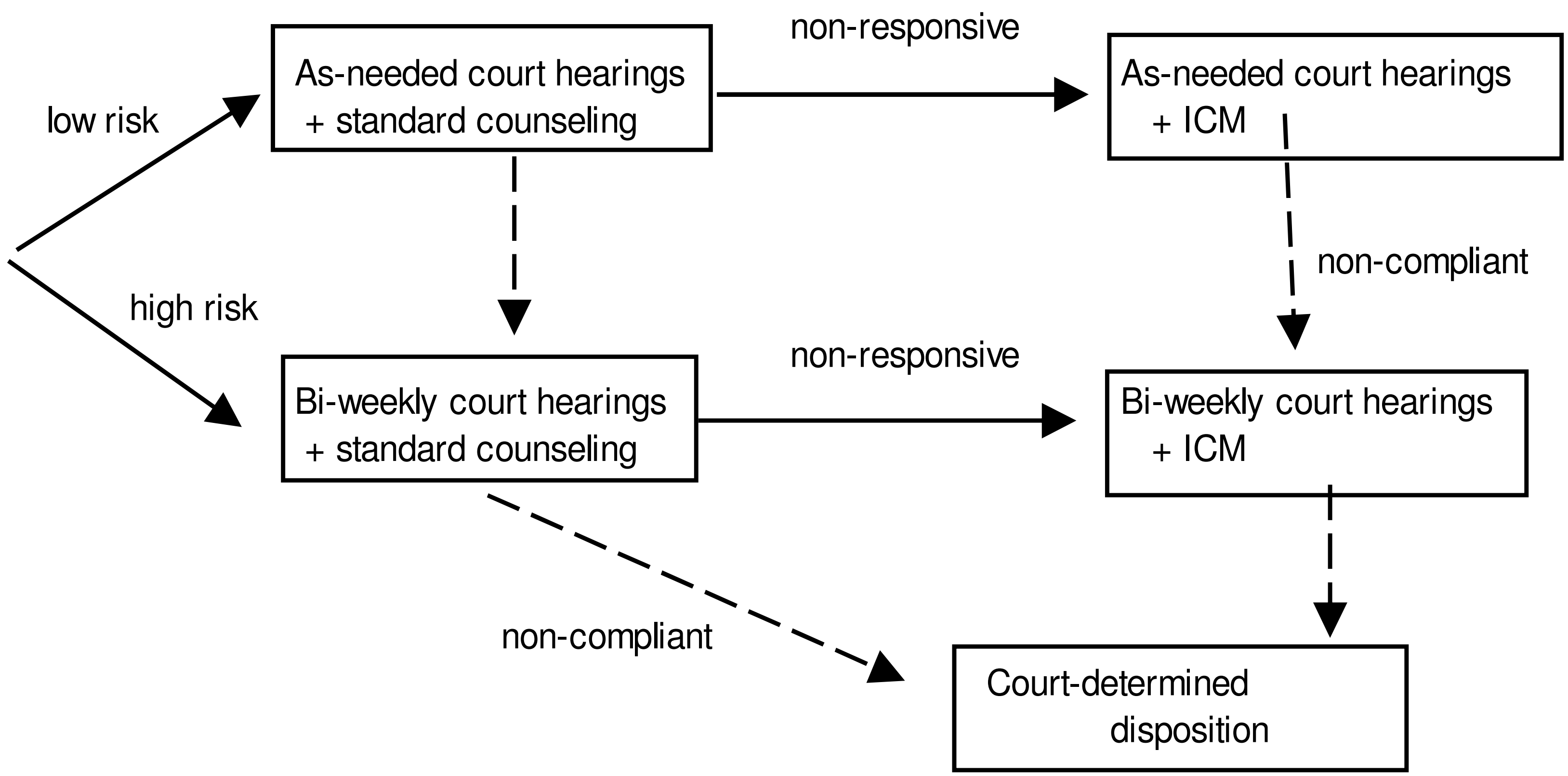
Why Adaptive Interventions?

- 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 common)
- Lack of adherence or excessive burden is common

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, 2009, 2012)

Adaptive Drug Court Program



Some Critical Decisions

- 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?)

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SMART Studies

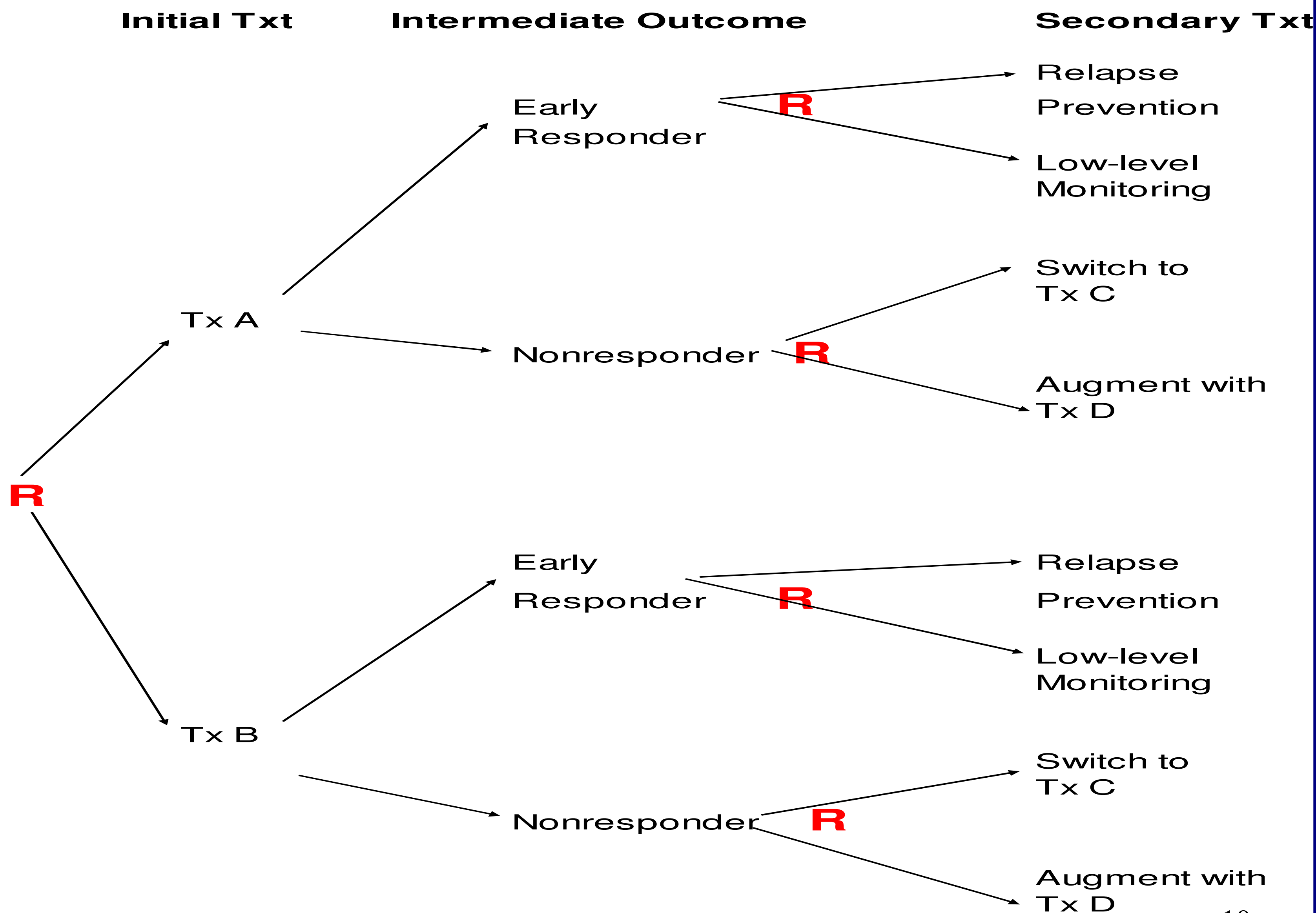
What is a sequential, multiple assignment, randomized trial (SMART)?

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

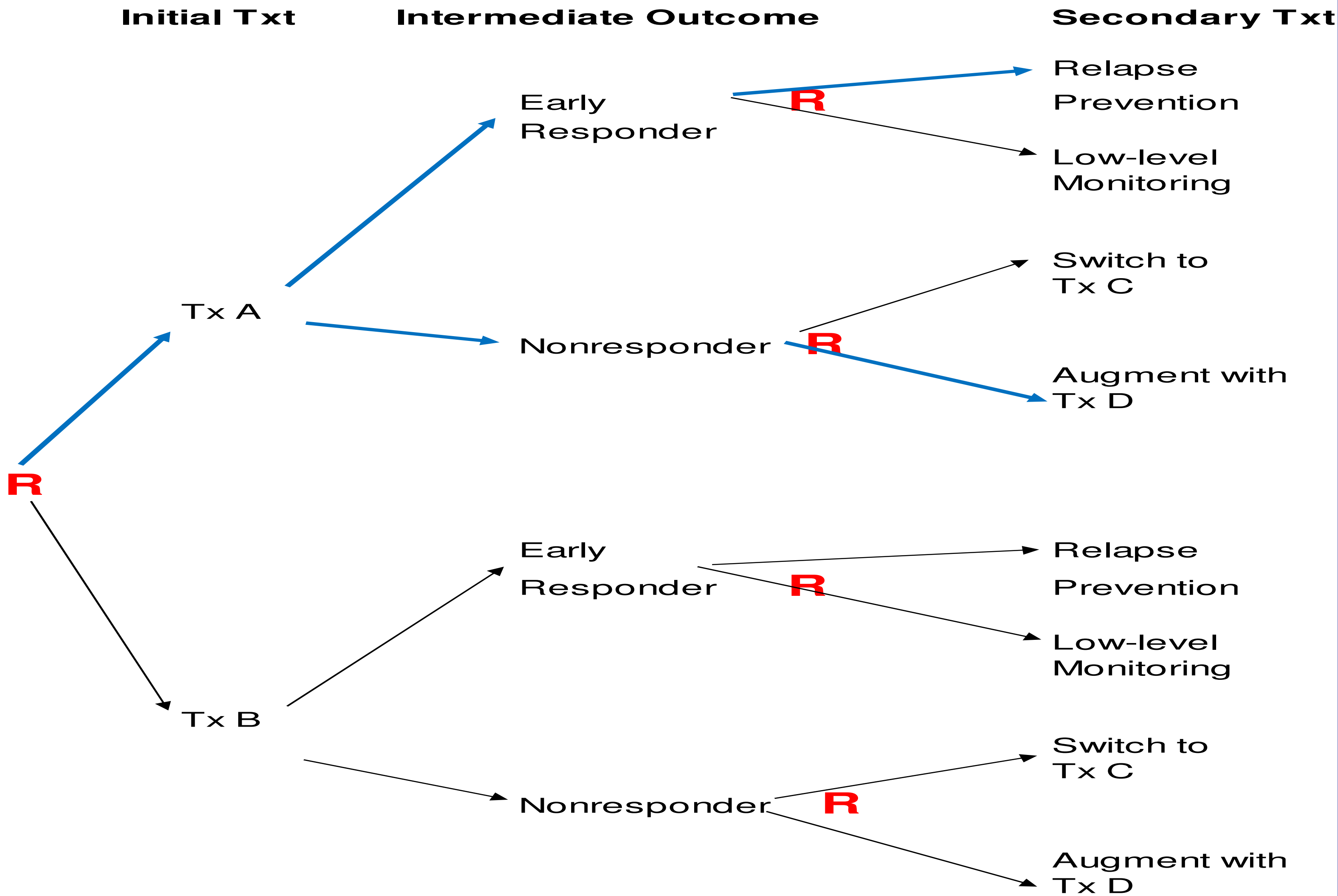
Each stage begins with a critical decision and a randomization to treatment takes place at each critical decision.

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

Sequential Multiple Assignment Randomization



An Adaptive Intervention in Blue



Alternate Approach to Constructing an Adaptive Intervention

- Why not use data from multiple trials to construct the adaptive intervention?
- Why not choose the best initial treatment on the basis of a randomized trial of initial treatments and why not choose the best secondary treatment on the basis of a randomized trial of secondary treatments?

Delayed Therapeutic Effects

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

Positive synergies: Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment. Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.

Delayed Therapeutic Effects

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

Negative synergies: Treatment A may produce a higher proportion of responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond. Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.

Prescriptive Effects

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

Treatment A may not produce as high a proportion of responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.

Sample Selection Effects

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

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

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 single-stage randomized trials may yield information about different populations from SMART trials.

Examples of "SMART" designs:

•Pelham (2012) Treatment of ADHD

•Oslin (primary analysis) Treatment of Alcohol Dependence

•Kasari (primary analysis, in field) Treatment of Children with Autism

•McKay (in field) Treatment of Alcohol and Cocaine Dependence

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

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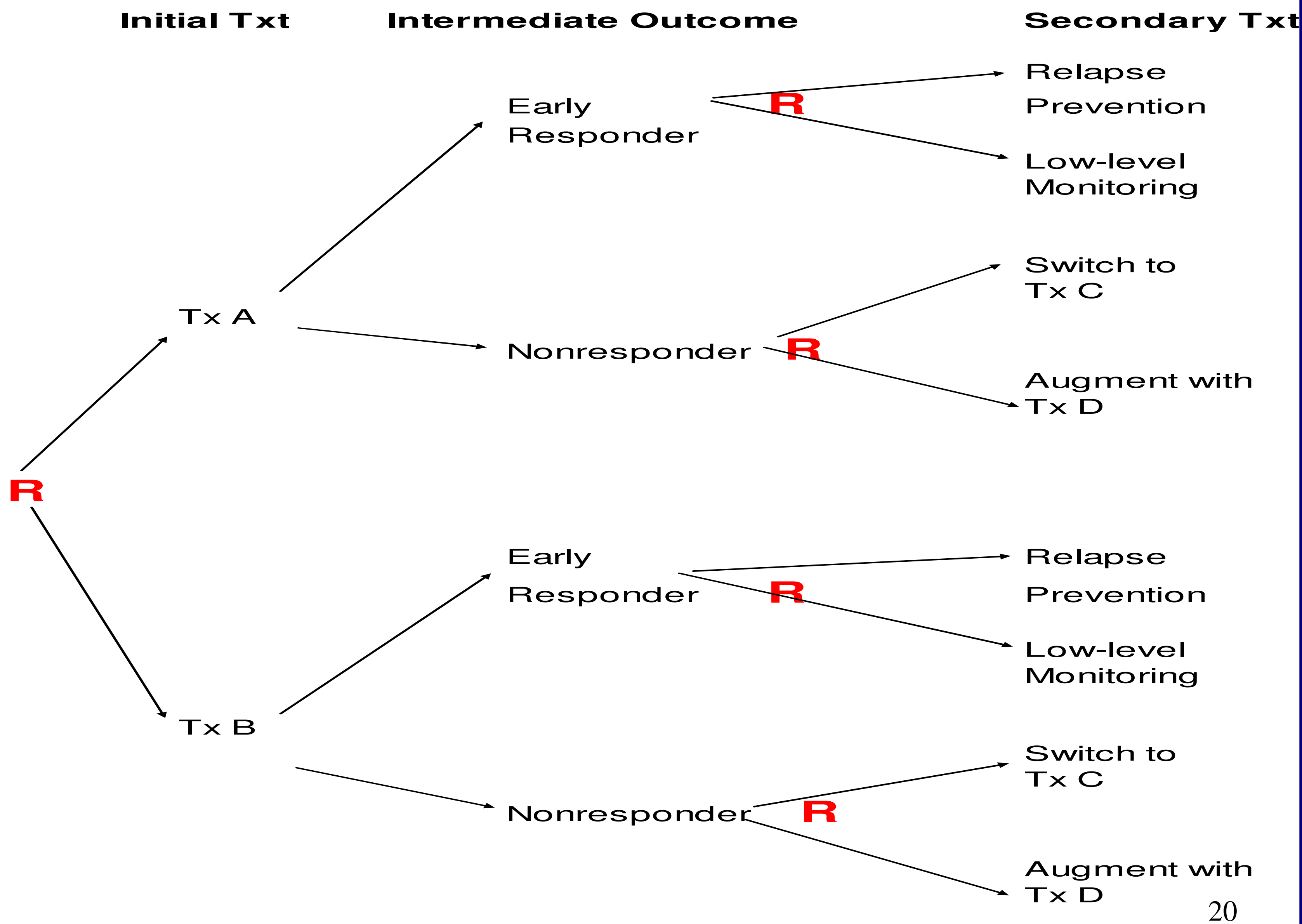
Sequential Multiple Assignment Randomization



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.

SMART Design Principles

- Choose primary hypotheses that are both scientifically important and aid in developing the adaptive intervention.
  - Power trial to address these hypotheses.

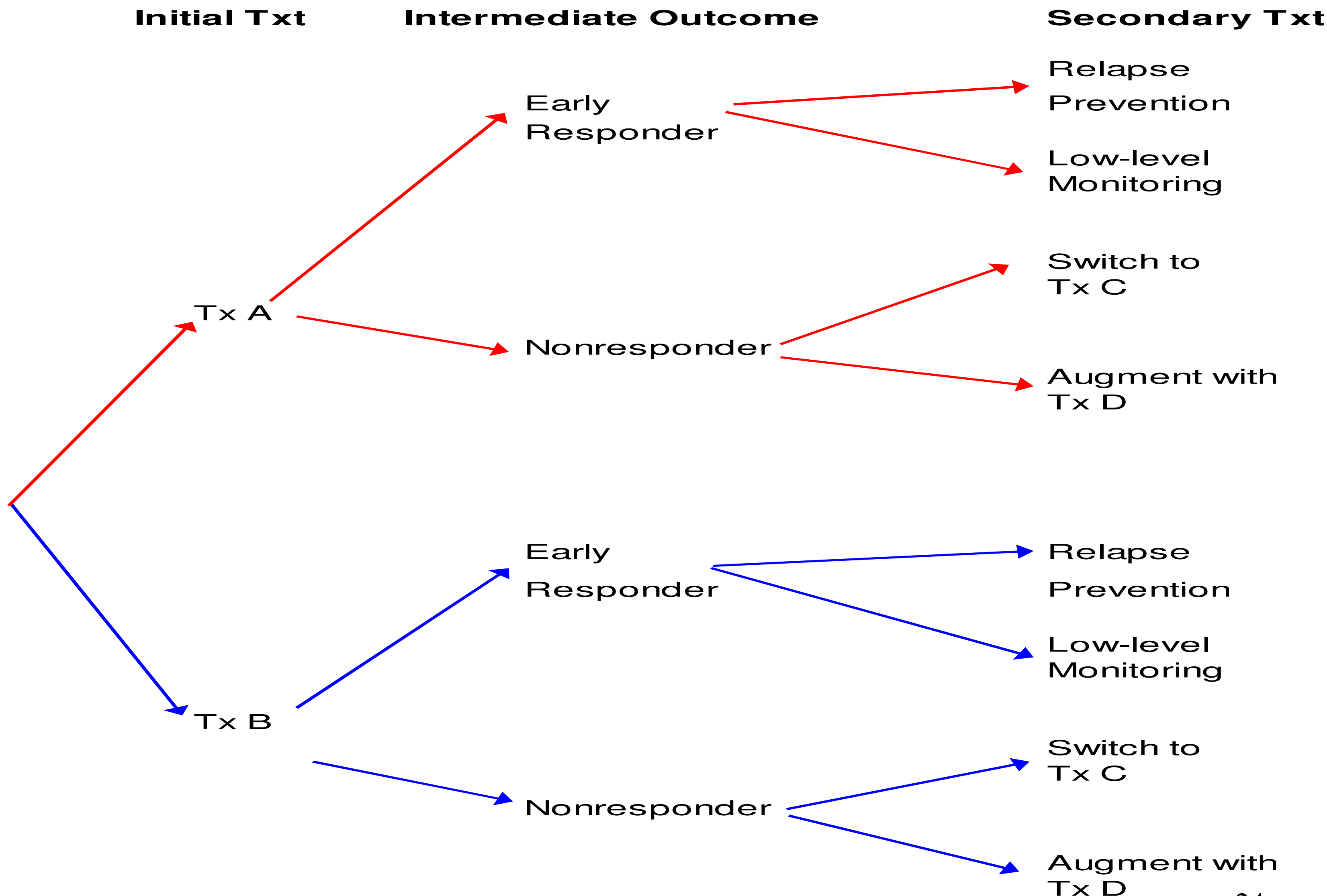
- Conduct secondary analyses that further develop the adaptive intervention (take advantage of the randomization in eliminating confounding).

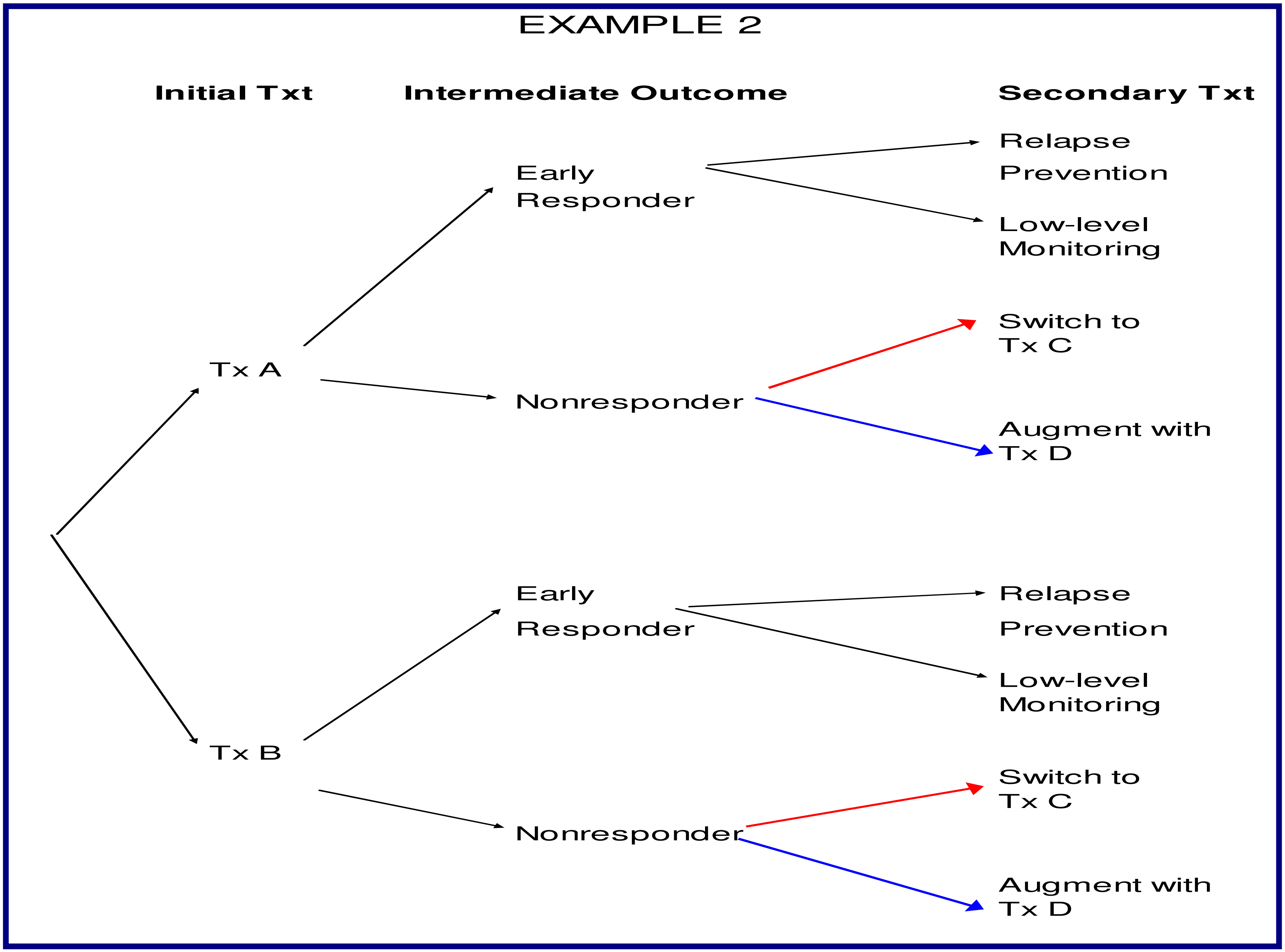
SMART Designing Principles: Primary Hypothesis

•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.

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


EXAMPLE 2
Initial Txt
Intermediate Outcome
Secondary Txt
Tx A
Tx B
Early Responder
Nonresponder
Early Responder
Nonresponder
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

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.*

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

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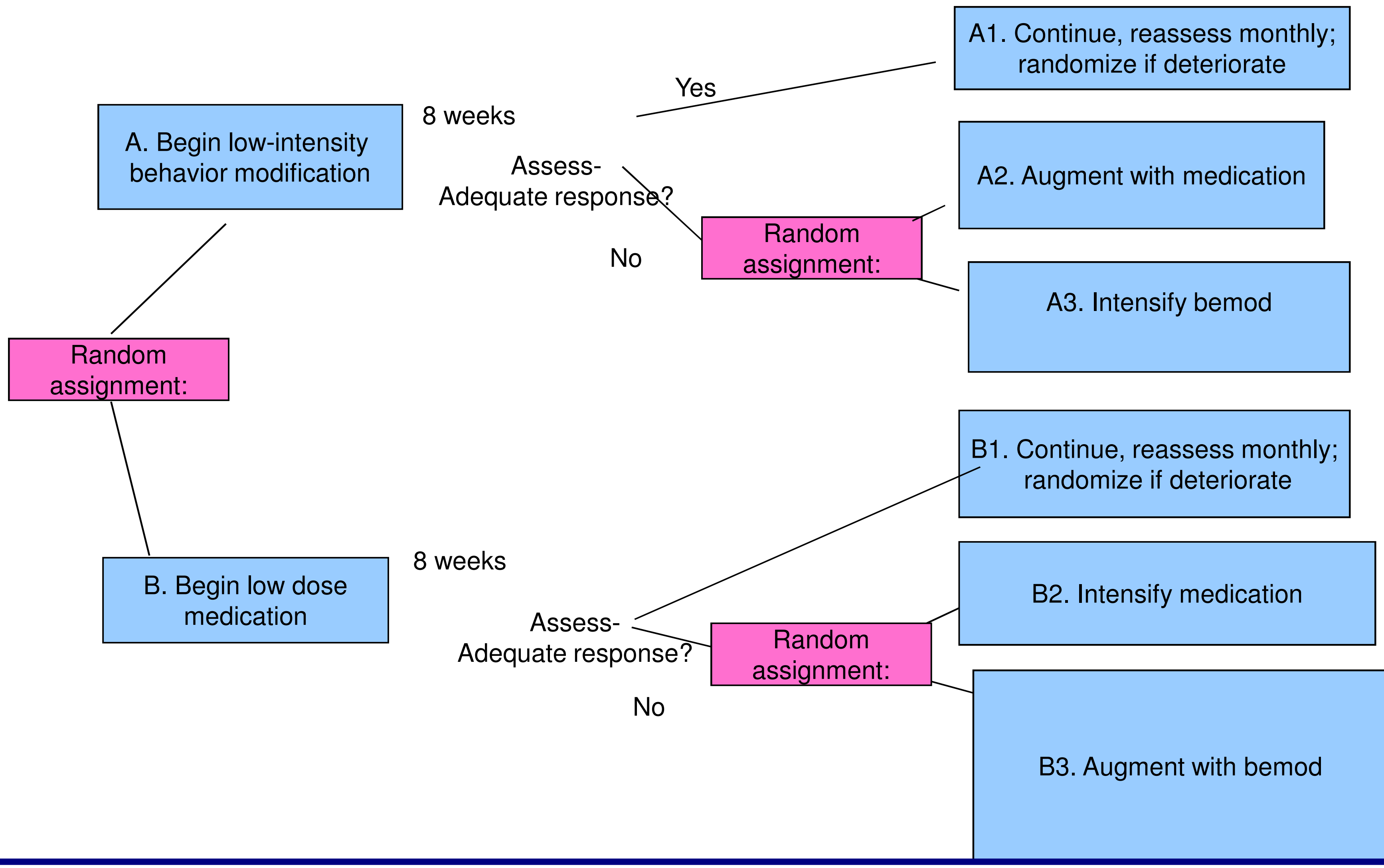
Pelham ADHD Study



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.

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

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 ($R_1=0$).

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, $\hat{Y}$

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)

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?

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

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)

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:

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

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

$$+ |\widehat{\beta}_{21} + \widehat{\beta}_{22} A_1 + \widehat{\beta}_{23} S_2|$$

Q-Learning using data on children with ADHD

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

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

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

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

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.

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.

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)

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)

2^{nd} 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.

Discussion

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

http://methodology.psu.edu/downloads

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

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.

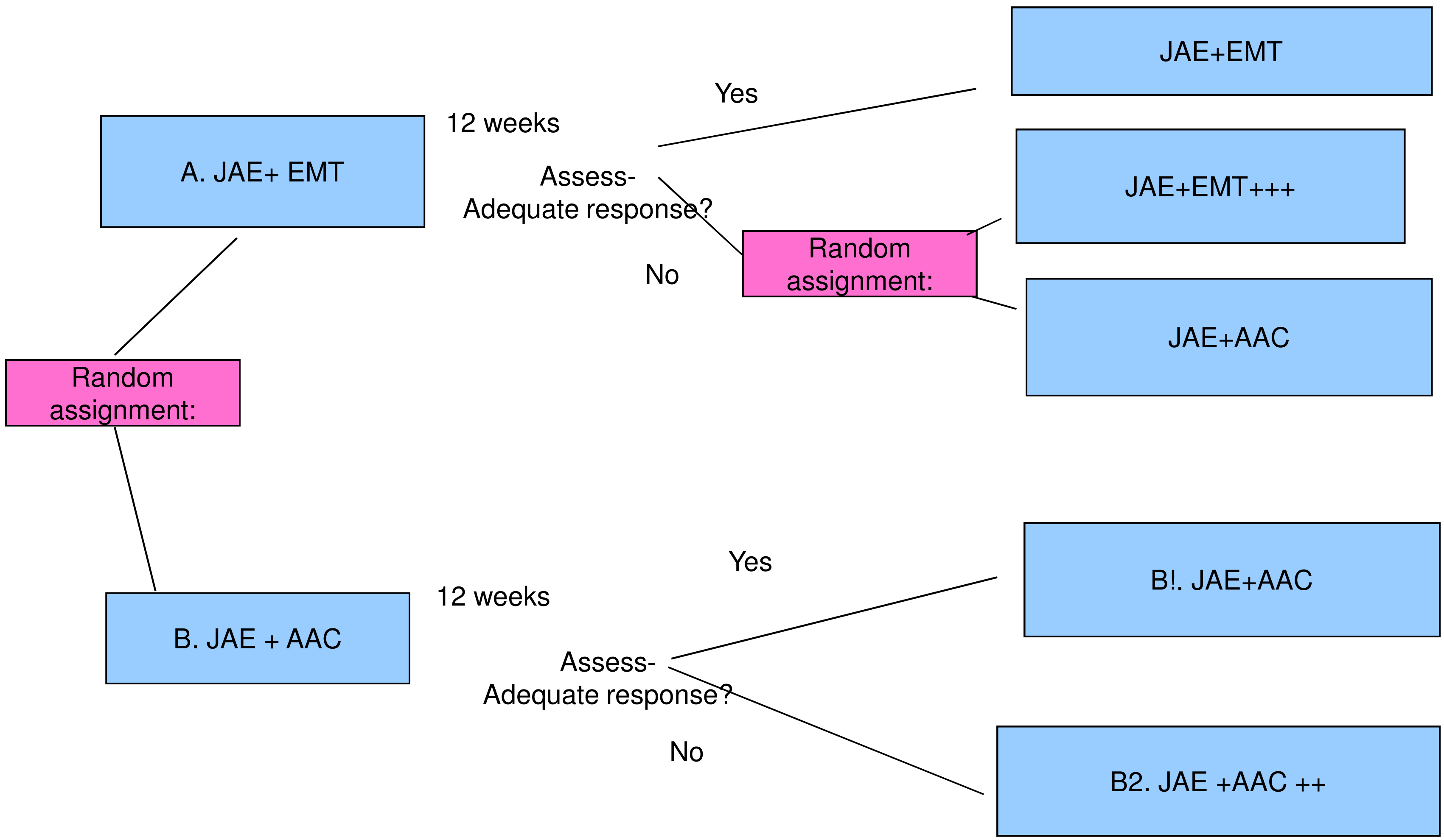
This seminar can be found at:

http://www.stat.lsa.umich.edu/~samurphy/seminars/CAPS.10.24.13.pdf

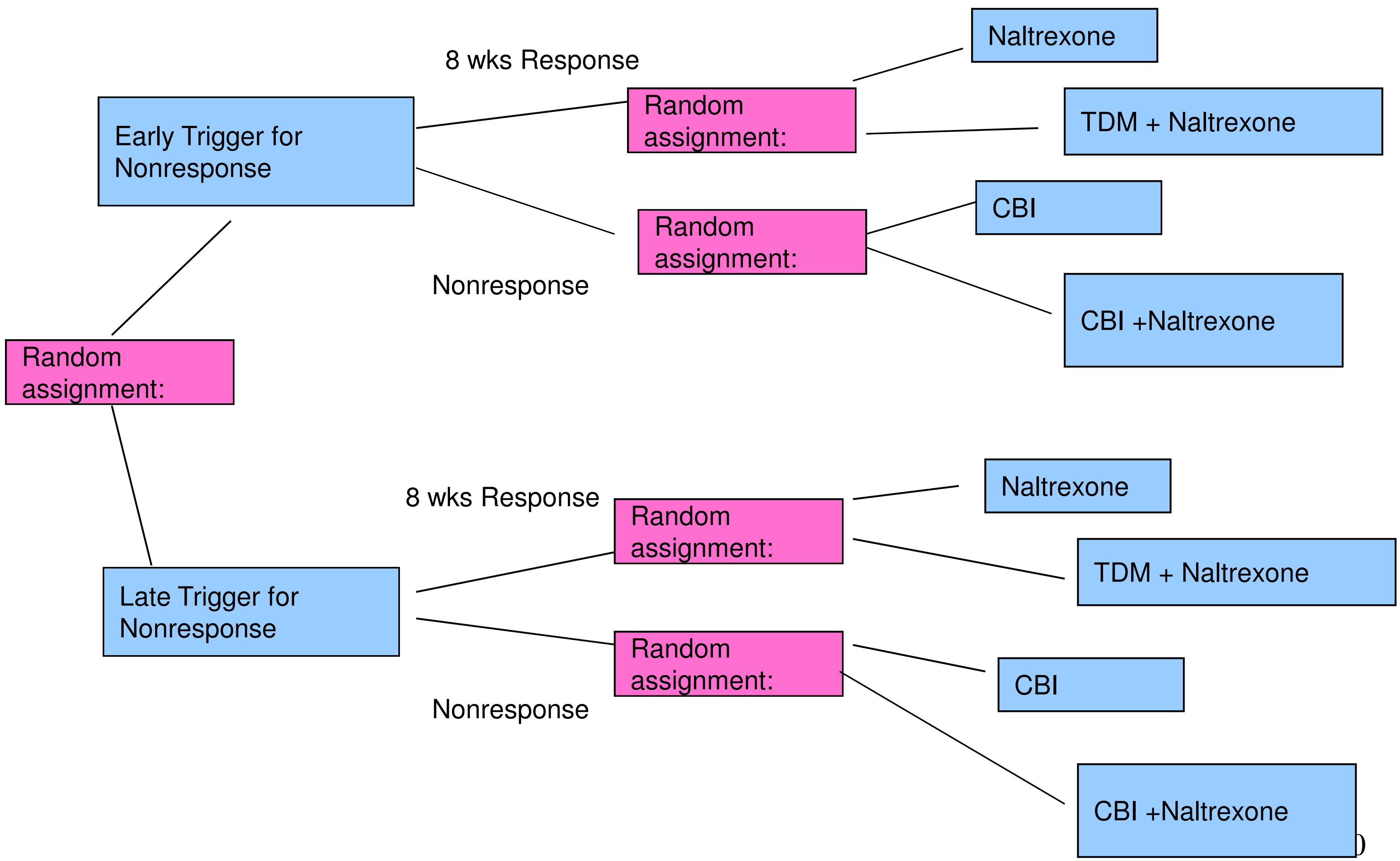
This seminar is based on work with many collaborators, some of which are: L. Collins, E. Laber, M. Qian, D. Almirall, K. Lynch, J. McKay, C. Kasari, H. Jones, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham. Email with questions or if you would like a copy:

samurphy@umich.edu

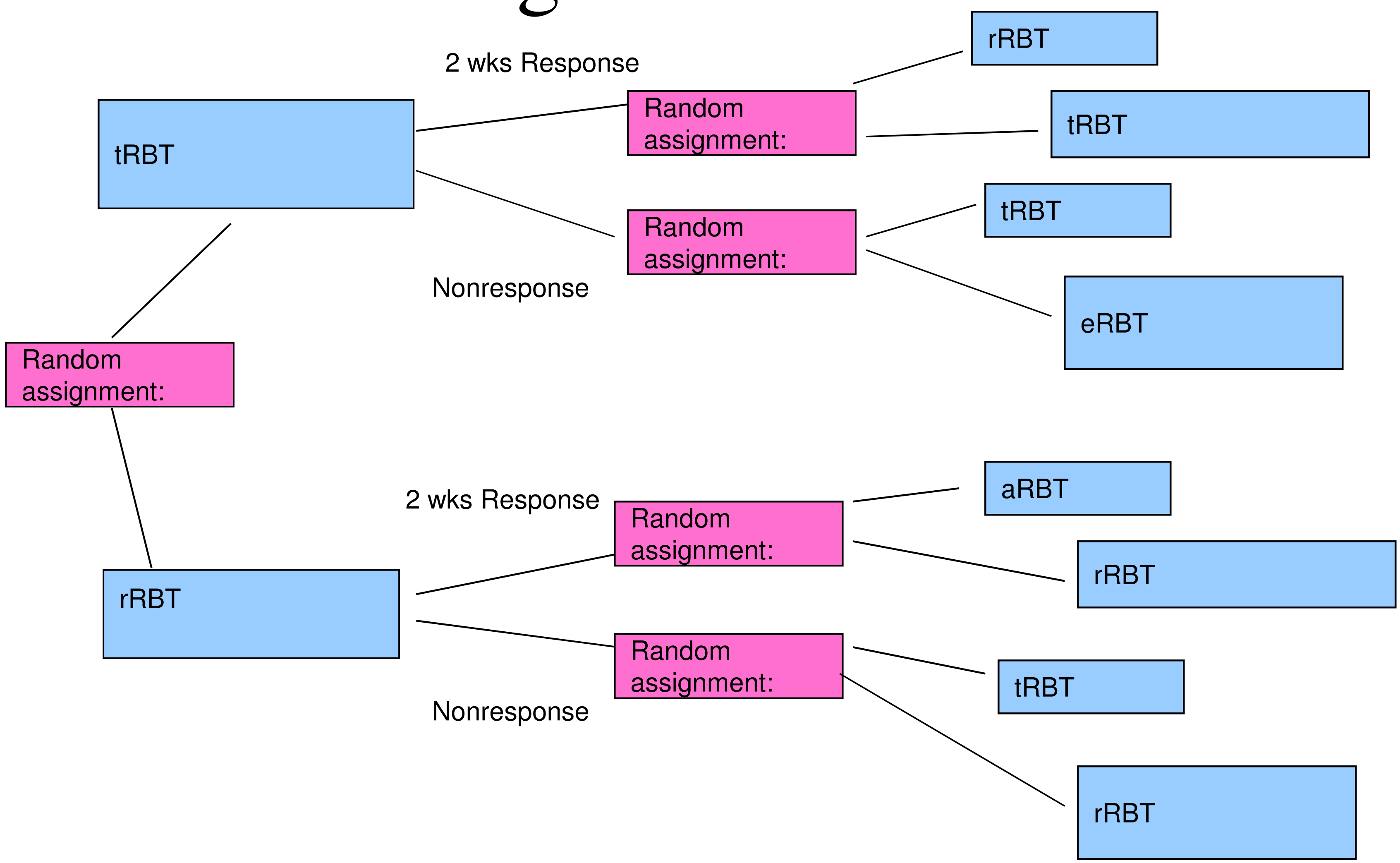
Kasari Autism Study



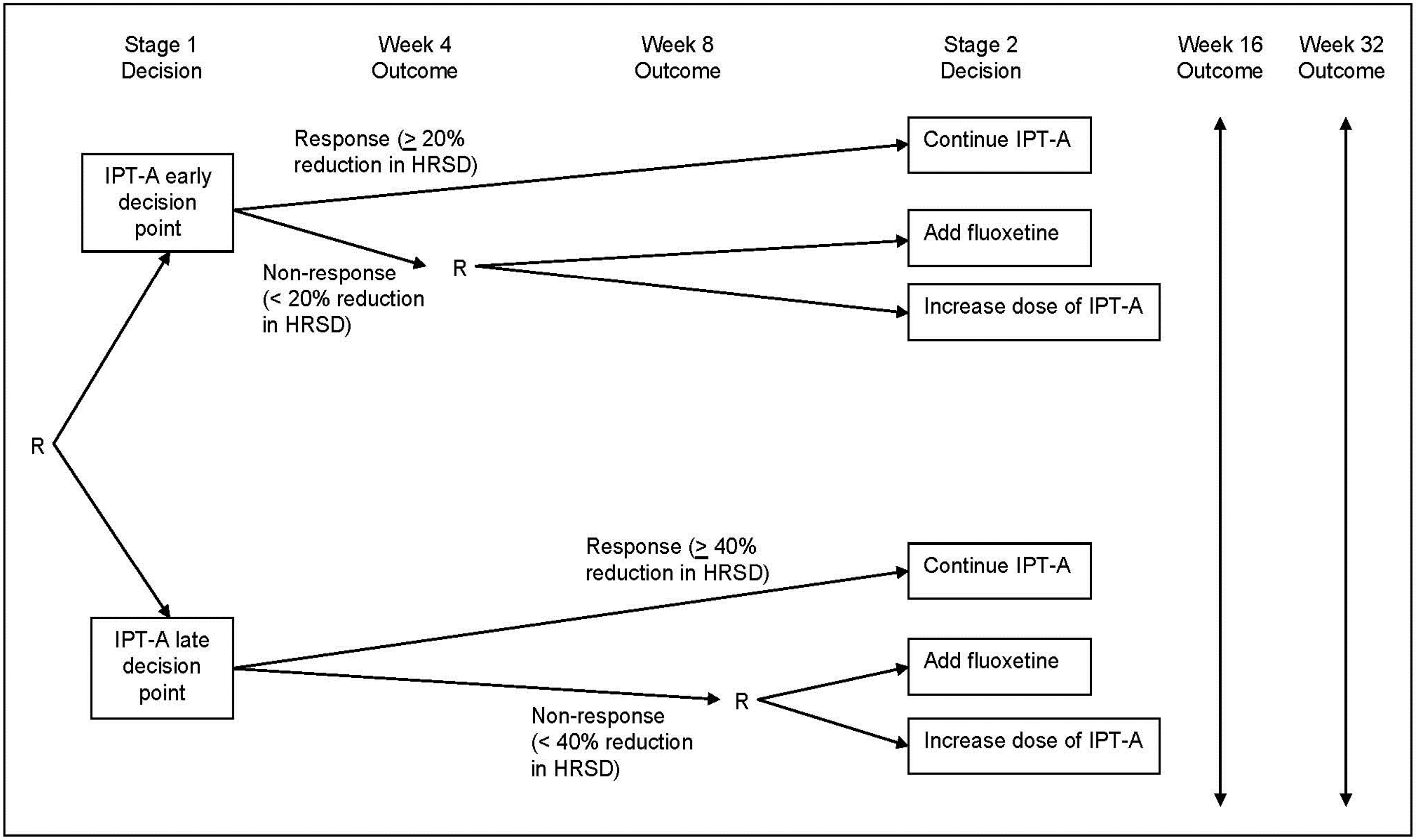
Oslin's ExTENd Study



Jones' Study for Drug-Addicted Pregnant Women

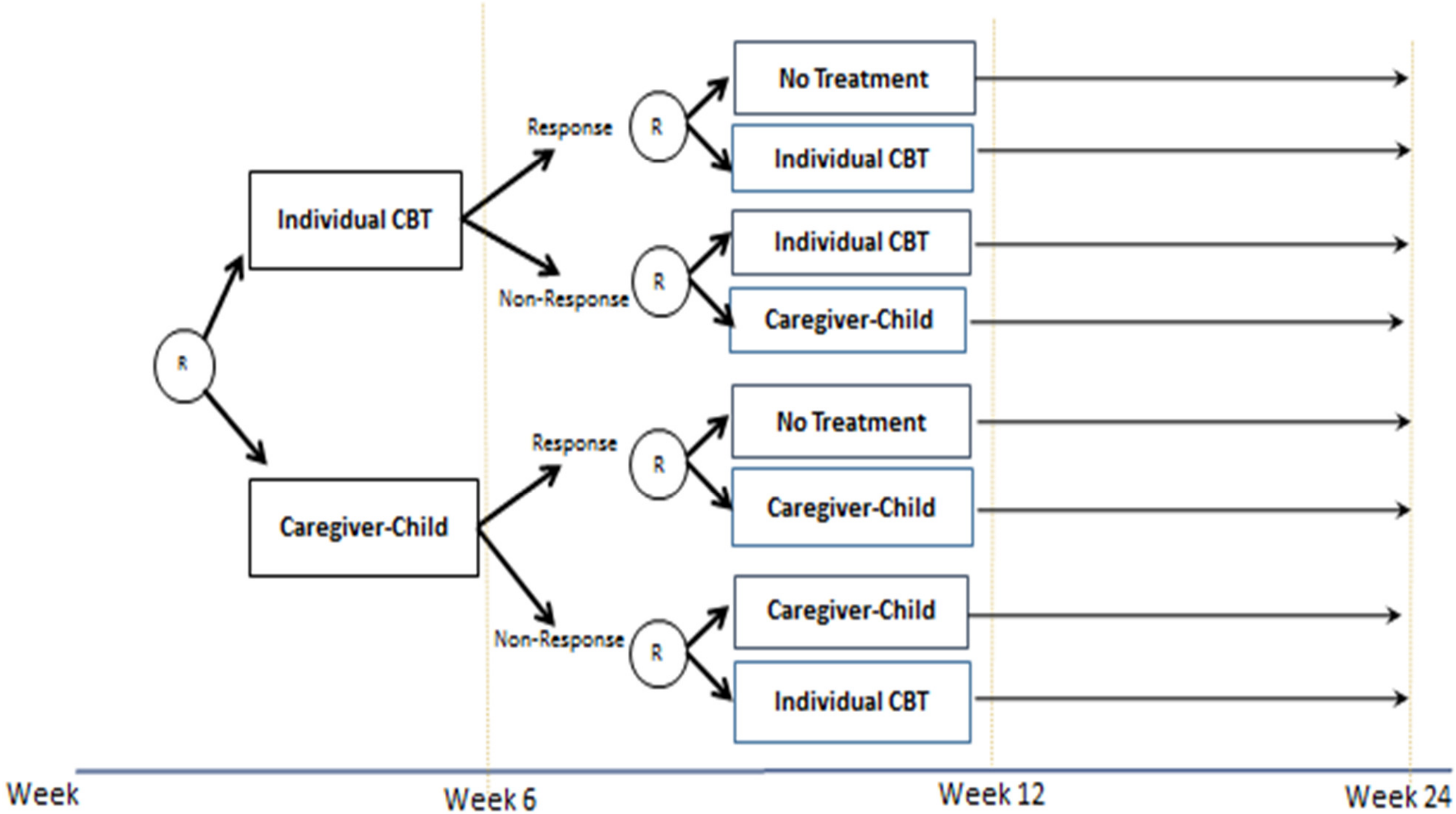


SMART for Adolescent Depression



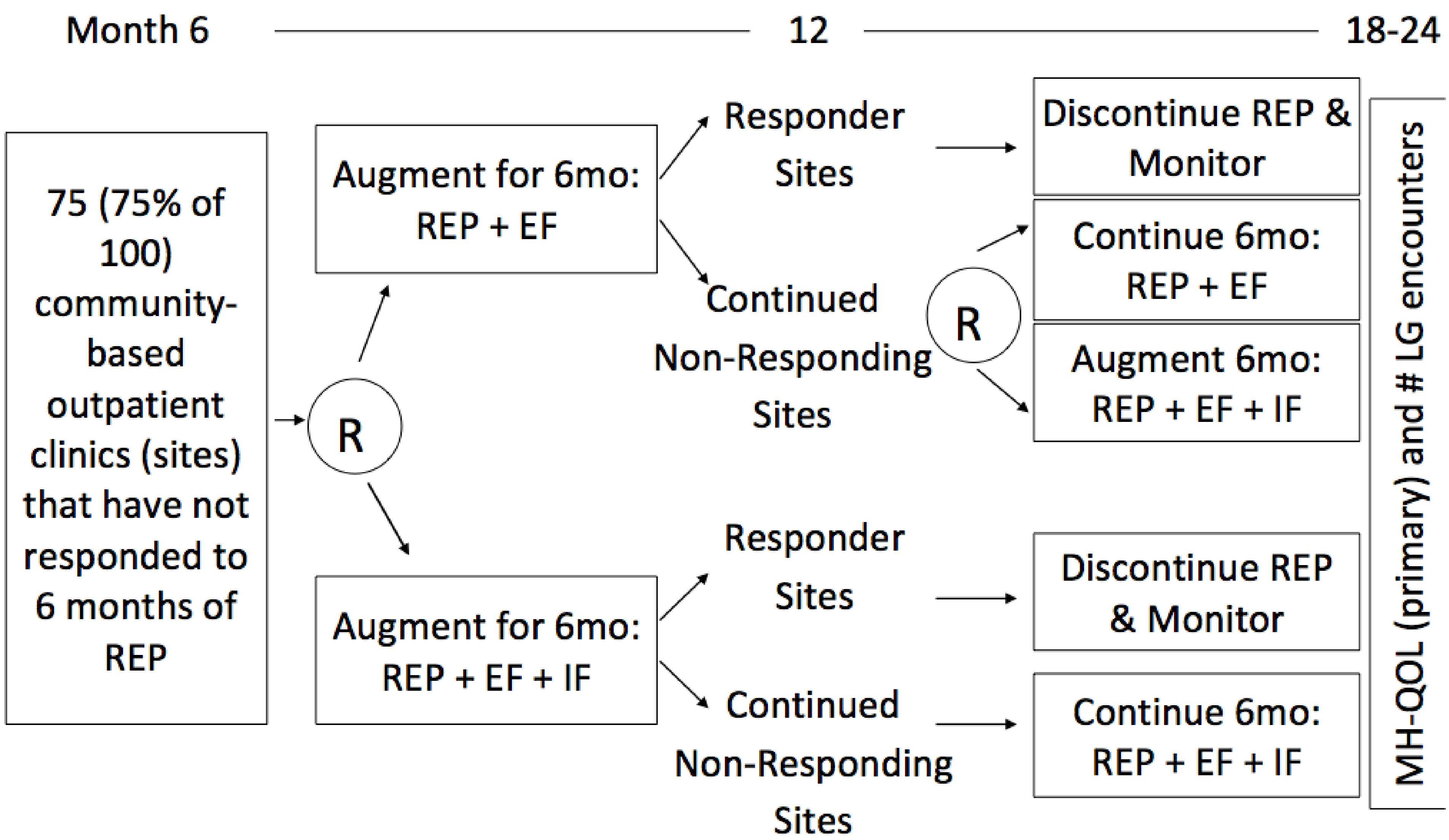
PI: Meredith Gunlicks-Stoessel, Univ of Minnesota (NIMH K23)

SMART for Child Depression



PI: Dikla Eckshtain, Harvard University (NIMH K23)

SMART REP



PI Amy Kilbourne

Figure 3: SMART Design