

Adaptive Interventions: Healing with Data

S.A. Murphy

Henry Seeley White Lecture

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Institute for Social Research
Survey Research Center



The Methodology Center
advancing methods, improving health



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 treatments, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

- Kasari et al. (2014) Treatment of Autism
- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008, 2012) Drug Court
- Adams et al. (2013) Improving Physical Activity

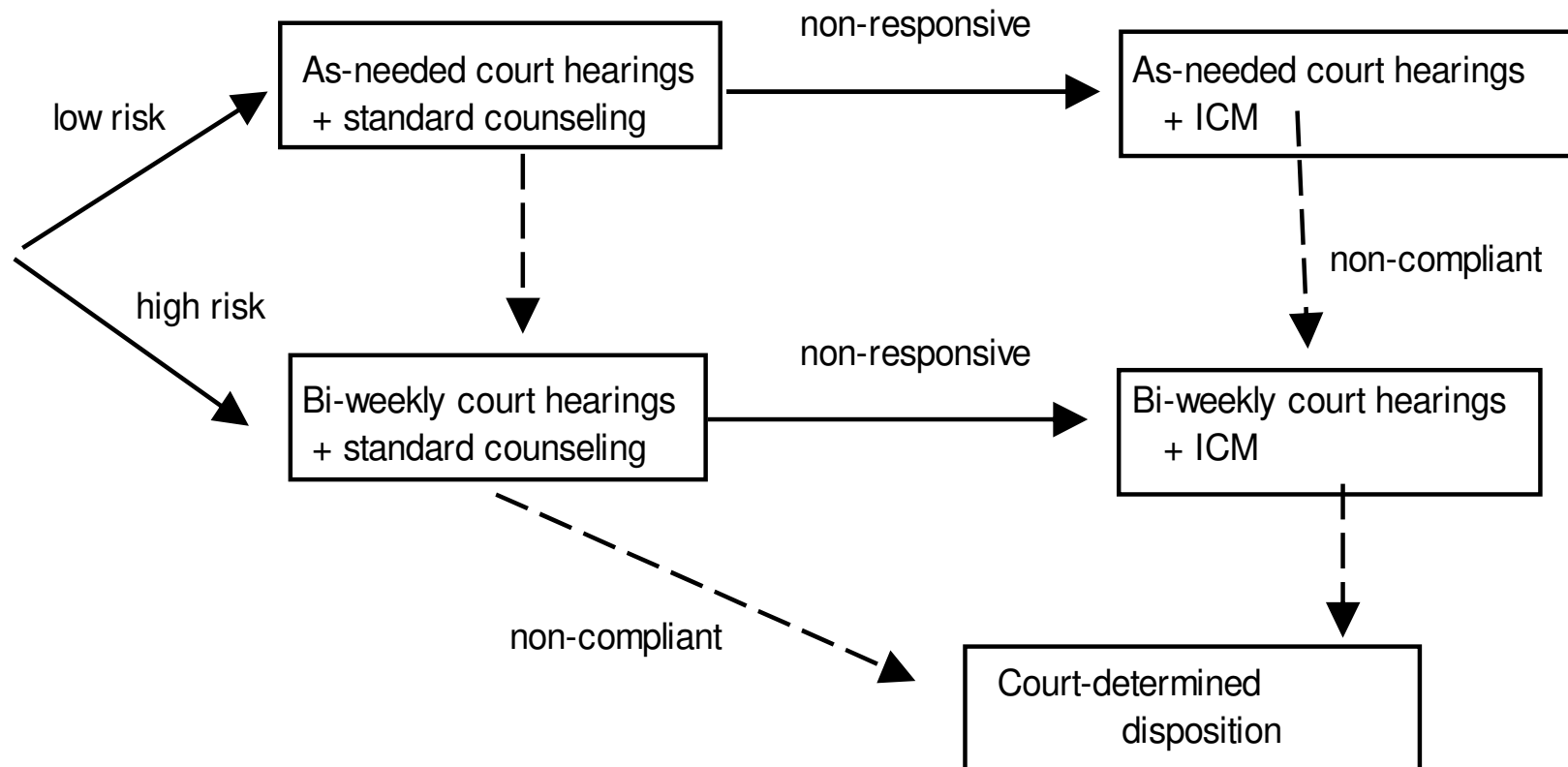
Why Adaptive Interventions?

- 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 (→ relapse)
- Excessive burden (→ non-adherence) 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?
(AKA: how do we individualize the sequence of treatments to the person?)

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SMART Studies

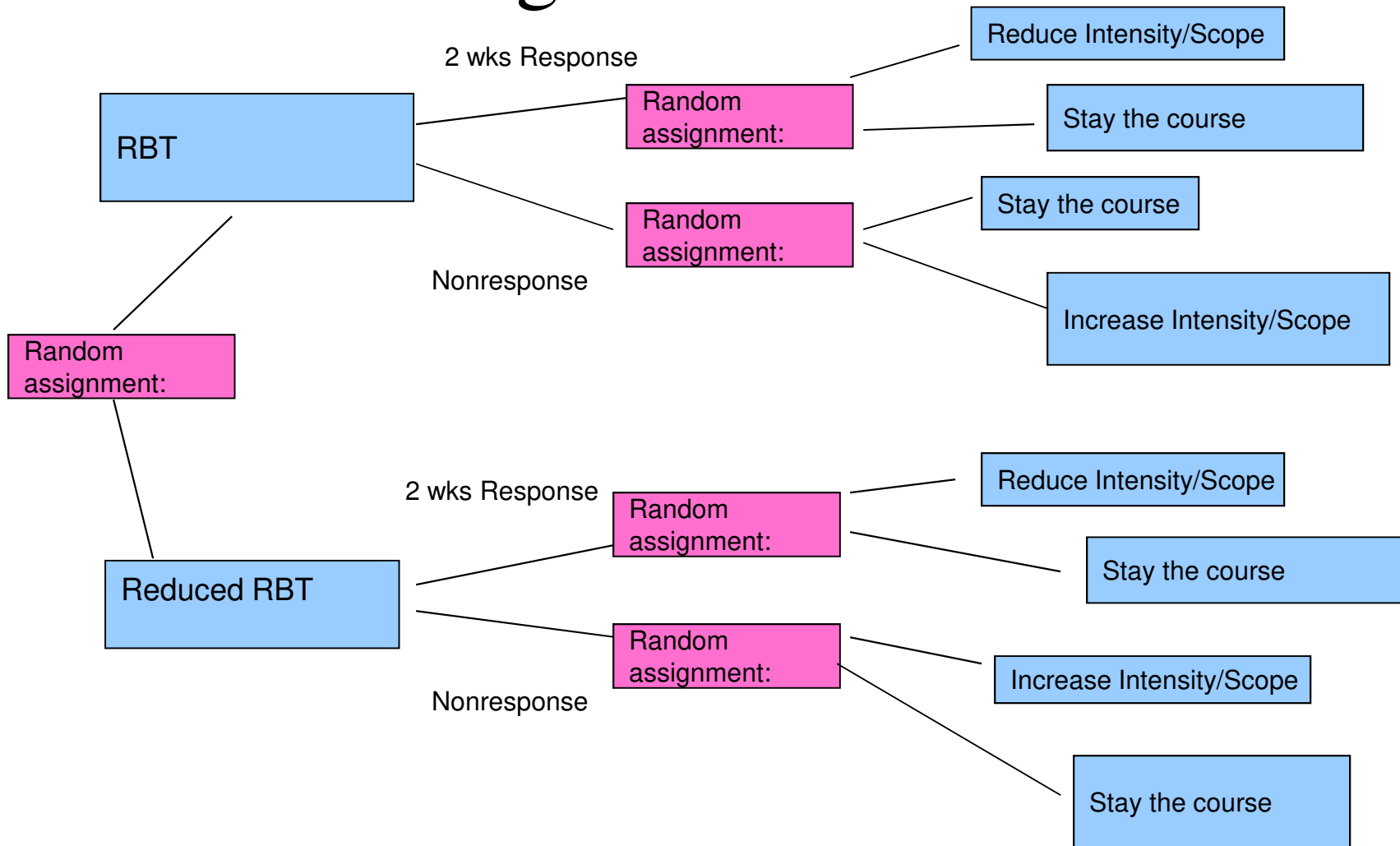
What is a sequential, multiple assignment, randomized trial (SMART)?

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

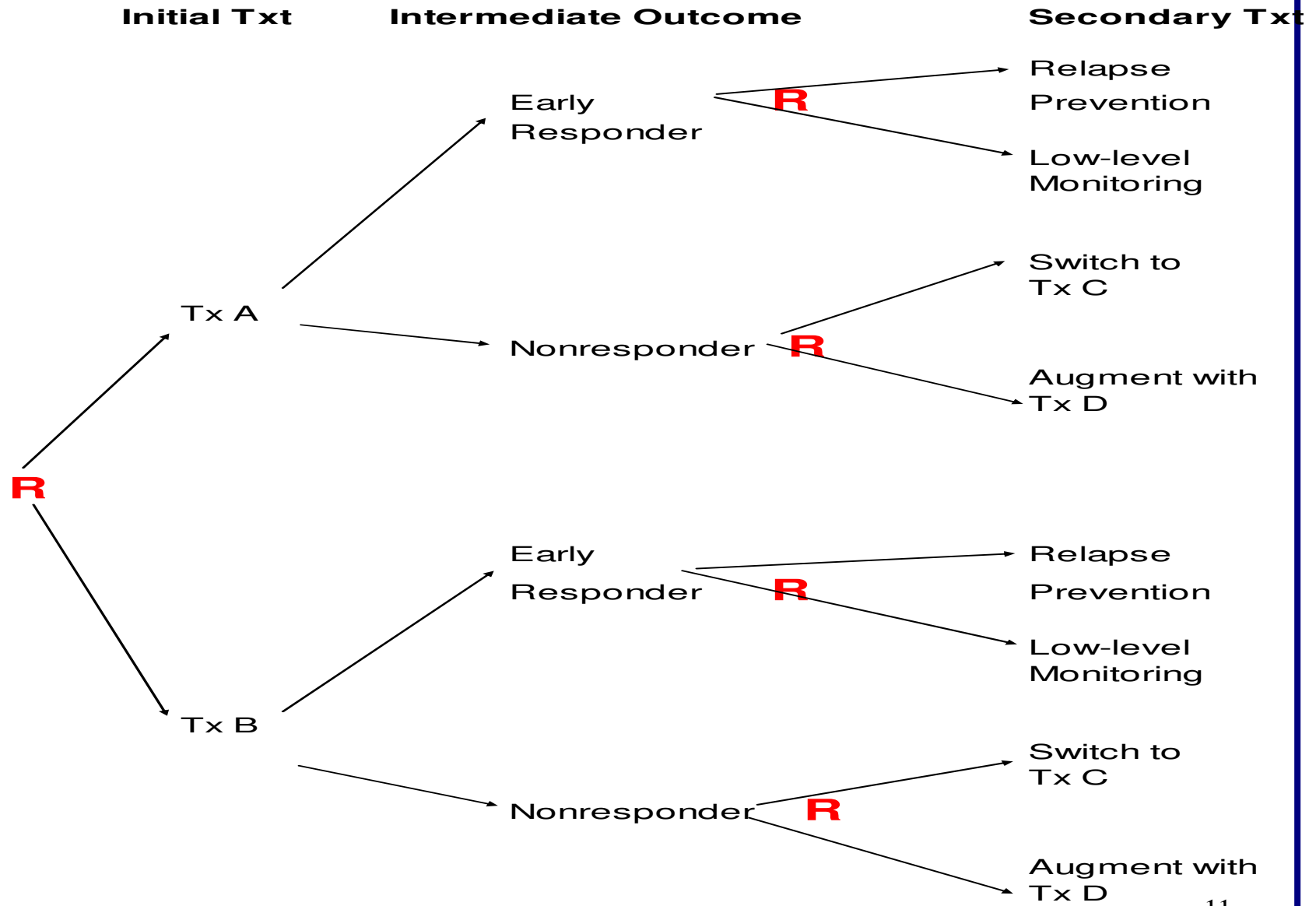
Each stage concerns a critical decision and randomization takes place at each critical decision.

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

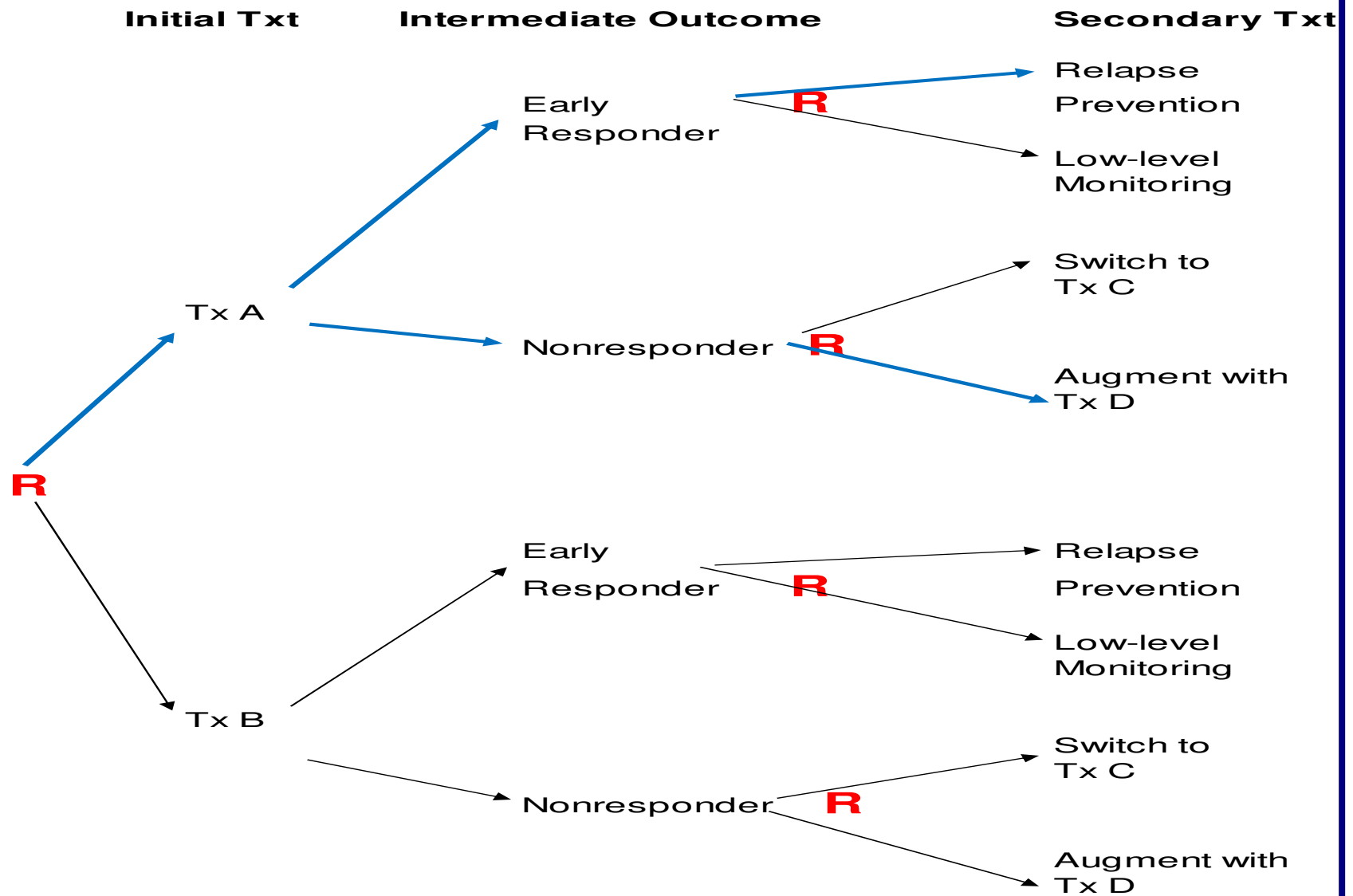
Jones' Study for Drug-Addicted Pregnant Women



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?
- 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.

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.

Sample Selection Effects

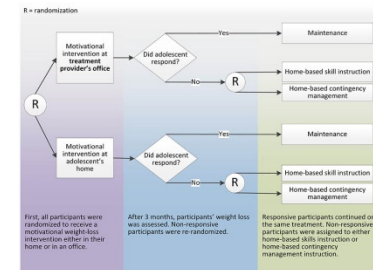
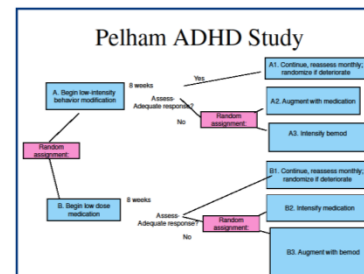
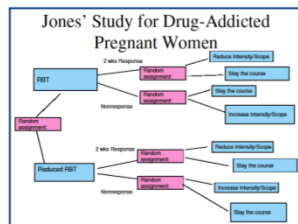
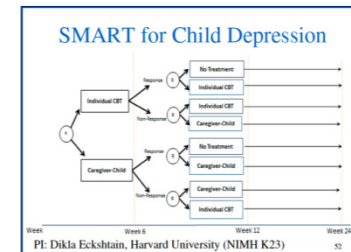
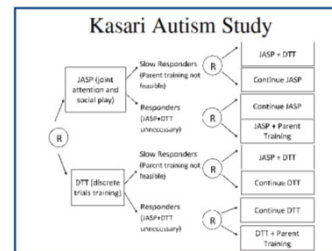
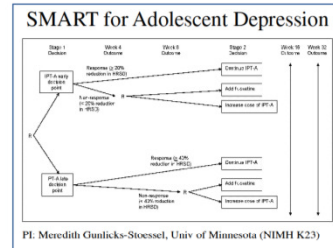
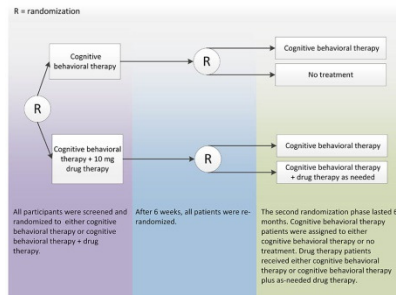
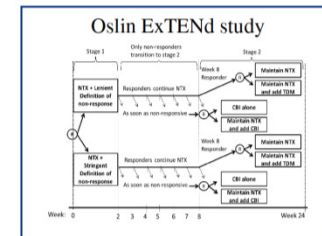
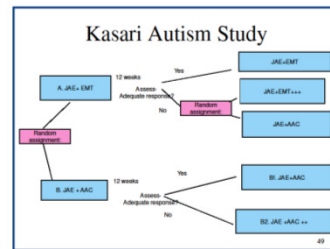
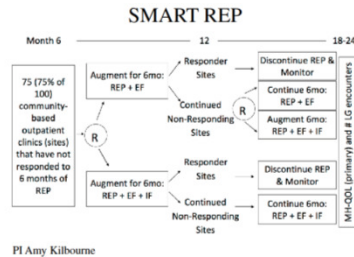
Why not use data from multiple trials to construct the adaptive intervention?

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, that are to be used as part of *a sequence of treatments*, we need to take into account the effects of the secondary treatments thus SMART
- Standard single-stage randomized trials may yield information about different populations from SMART trials.

Sequential, Multiple Assignment, Randomized Trials



<https://methodology.psu.edu/ra/adap-inter/projects>

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SMART Design Principles

- Select the Critical Decisions
- **Aim for Simplicity:** 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.

SMART Design Principles

- Choose primary hypotheses that are both scientifically important and aid in developing the adaptive intervention.
 - Determine sample size (number of participants) so trial can be used to address these hypotheses.
- Conduct secondary analyses that further develop the adaptive intervention—these analyses use the randomization to eliminate confounding.

SMART Designing Principles: Primary Hypothesis

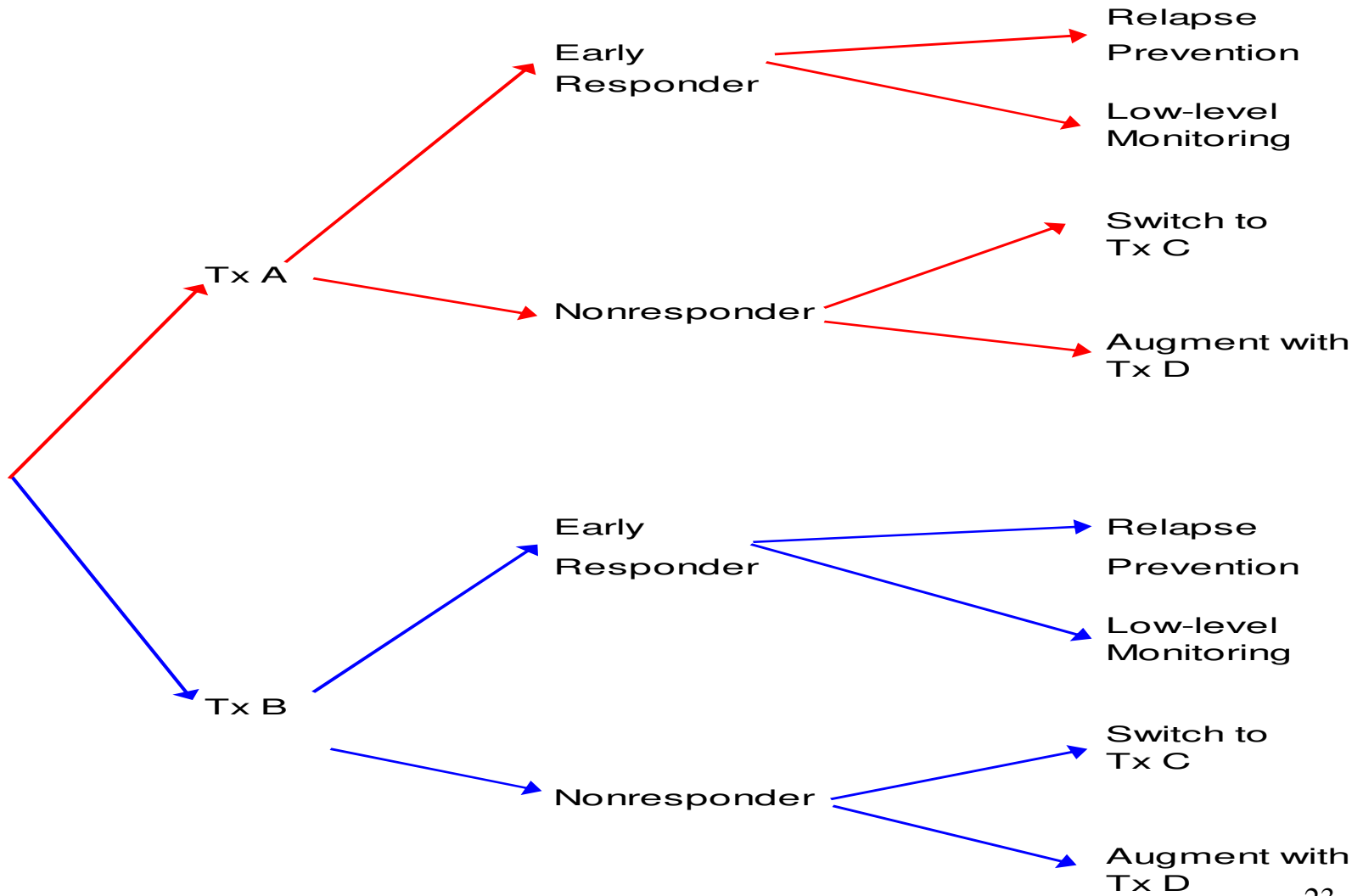
- EXAMPLE 1: (*sample size is highly constrained*):
Hypothesize that adaptive interventions beginning with treatment A result in lower symptoms than adaptive interventions beginning with treatment B.
- EXAMPLE 2: (*sample size is less constrained*):
Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.

EXAMPLE 1

Initial Txt

Intermediate Outcome

Secondary Txt

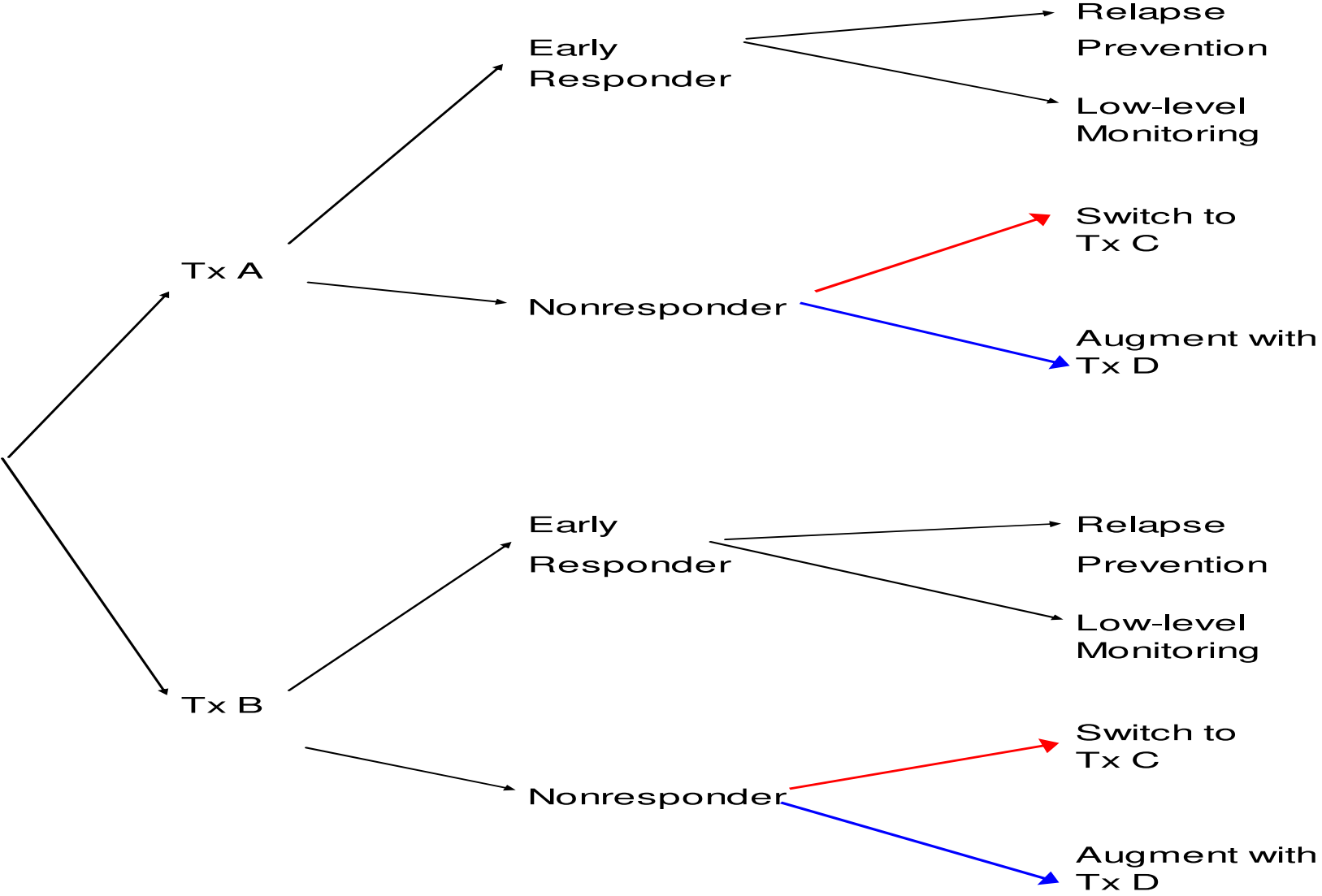


EXAMPLE 2

Initial Txt

Intermediate Outcome

Secondary Txt



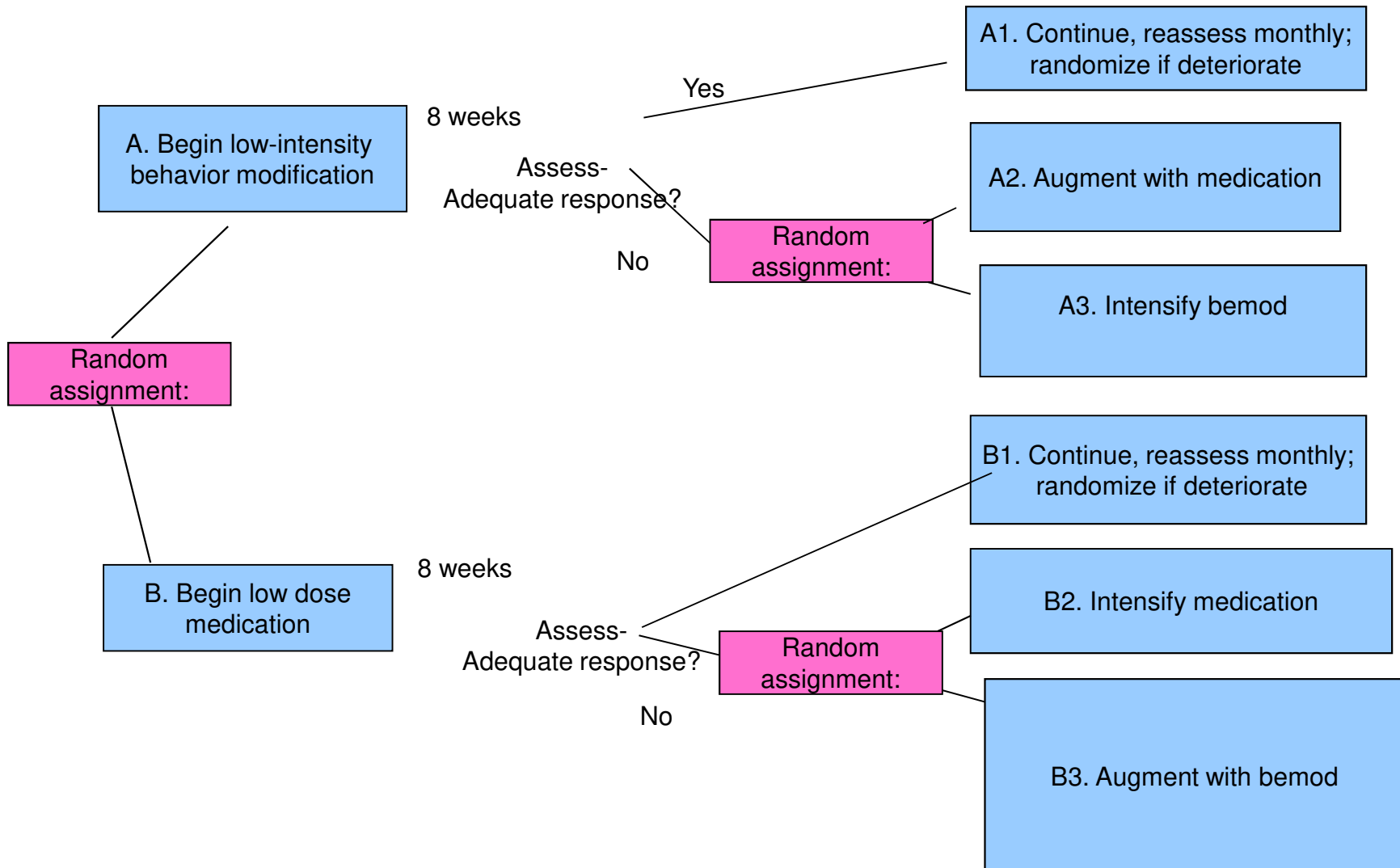
SMART Designing Principles: Sample Size Formula

- 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 is the 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 is same as for a two group comparison of non-responders.*

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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 might contrast the proposed adaptive intervention with standard practice.

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 is a predictor of end of school performance, Y , under optimal treatment in stage 2.
 - Stage 2 analysis is used to construct the predictor, \hat{Y} , of end of school performance, 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—prediction of end of school year performance 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, \hat{Y} for the Stage 1 Regression

Stage 1 dependent variable: $R_1Y + (1 - R_1)\hat{Y}$

where

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

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*. We need to quantify our uncertainty!
- 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 for second stage Treatment Effect
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

First State Treatment Decision: Positive Treatment Effect \rightarrow BMOD

	90% Confidence Interval for First Stage Treatment Effect
Prior MEDS	(-0.48, 0.16)
No Prior MEDS	(-0.05, 0.39)

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.

Our present work.....

- Increasing use of wearable computers (e.g smart phones, etc.) to both collect real time data and provide *just-in-time* adaptive interventions.
- We have developed study designs aimed at providing data for use in constructing and optimizing just-in-time adaptive interventions.
 - Participants are randomized 100's or 1000's of times in these designs.

This seminar can be found at:

<http://www.stat.lsa.umich.edu/~samurphy/seminars/Vassar.02.18.16.ppt>

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, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham! Email with questions or if you would like a copy:

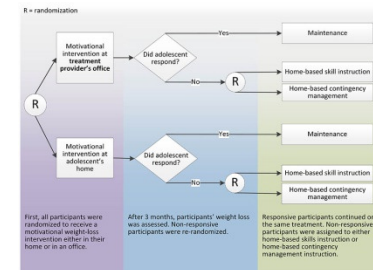
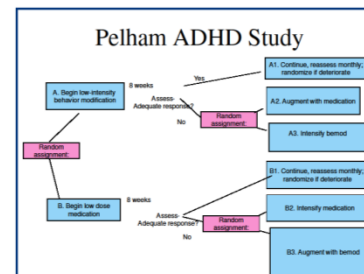
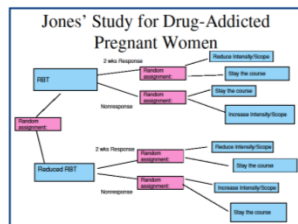
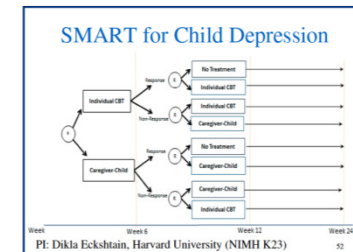
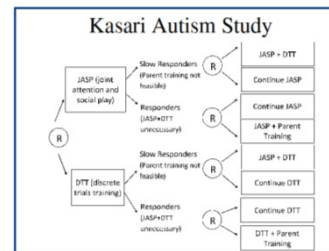
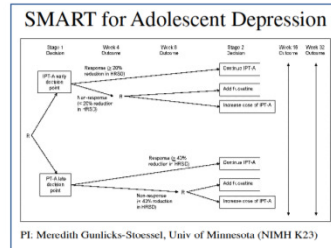
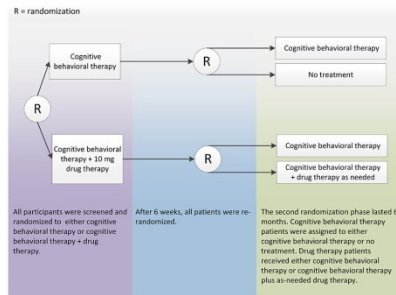
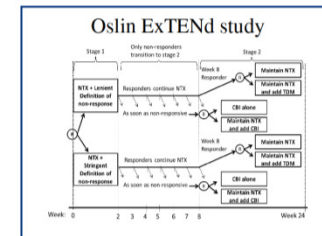
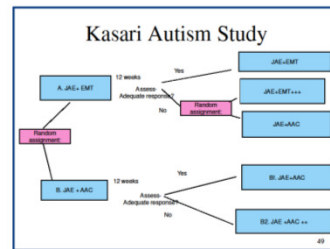
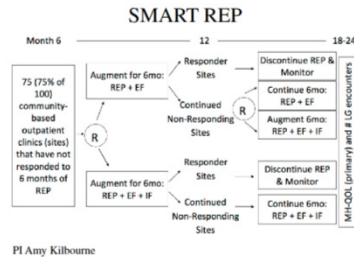
samurphy@umich.edu

Examples of “SMART” designs:

- Pelham (2012) Treatment of ADHD
- Oslin (2013) Treatment of Alcohol Dependence
- Kasari (multiple) Treatment of Children with Autism
- McKay (2015) Treatment of Alcohol and Cocaine Dependence
- Kilbourne (in field) “Treatment” to Improve Implementation of Effective Programs.

<http://methodology.psu.edu/ra/smart/projects>

Sequential, Multiple Assignment, Randomized Trials



<https://methodology.psu.edu/ra/adap-inter/projects>

Adaptive Implementation Intervention of “Replicating Effective Programs”

“Treatments”:

- External Facilitators (EF) and
- Internal Facilitators (IF)

Two Critical Decisions

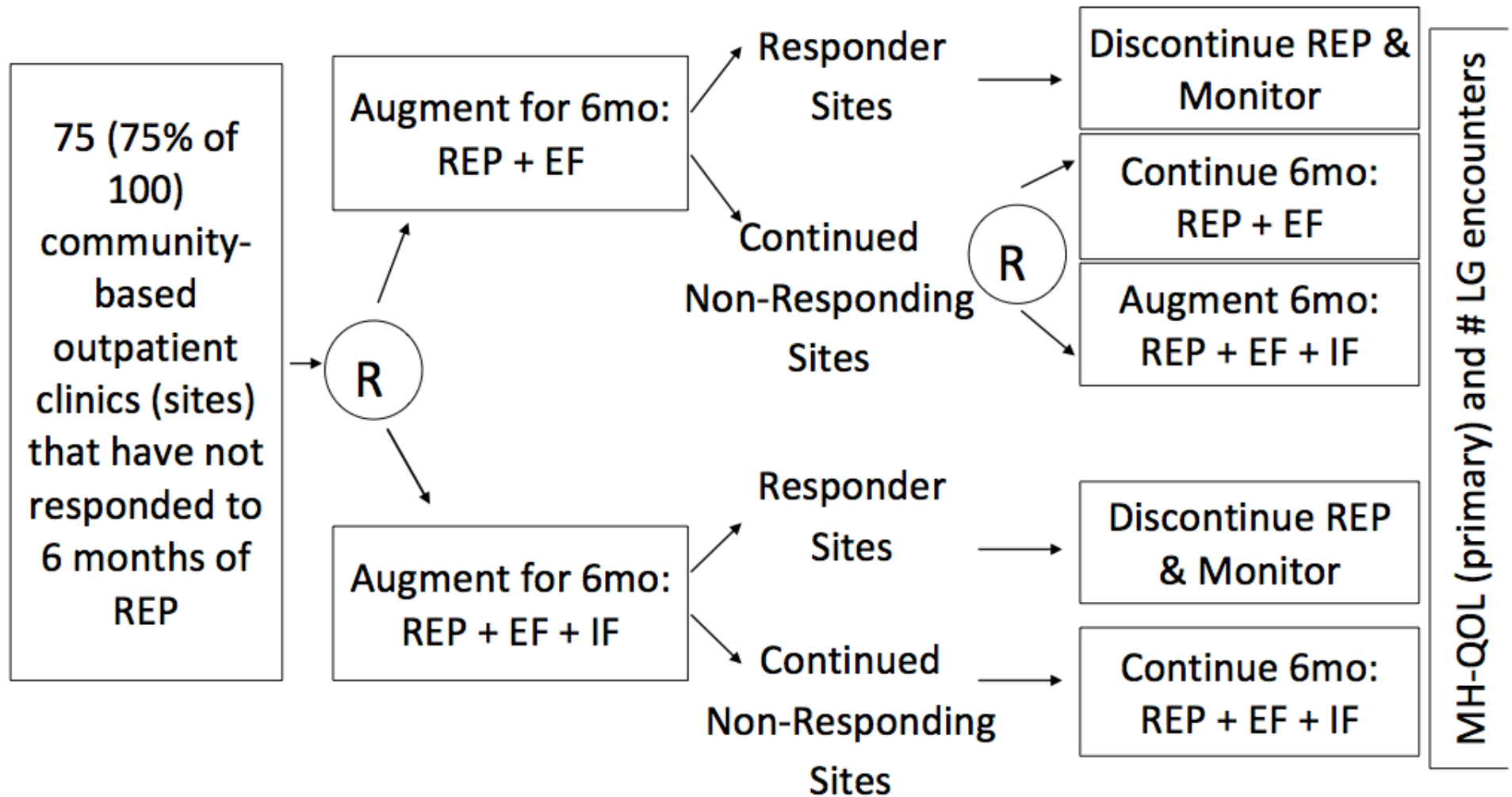
- (1) Which treatment to provide to sites that are insufficient responders to standard REP?
- (2) Which treatment to provide to the sites that continue to show non-response?

SMART REP

Month 6

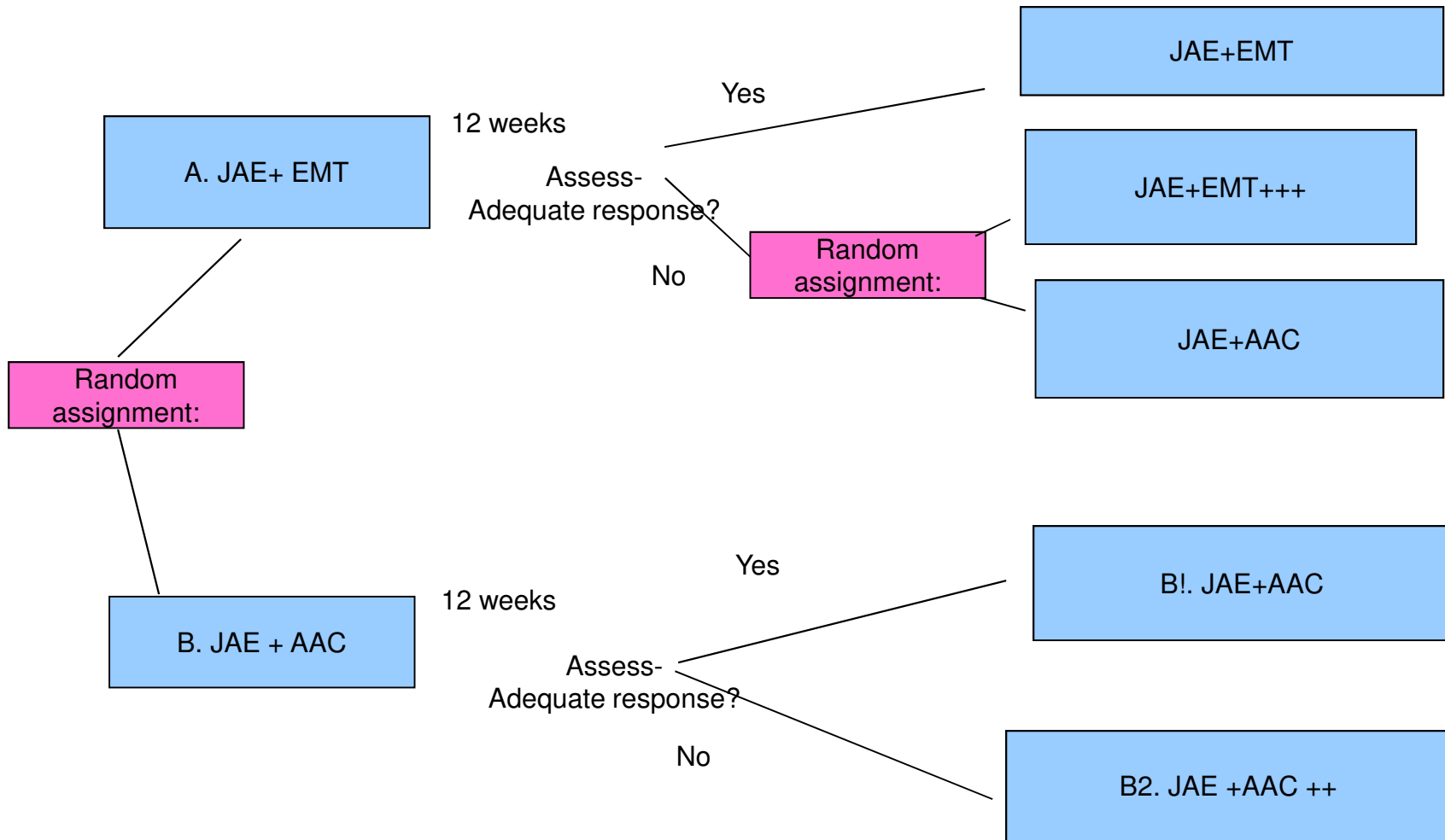
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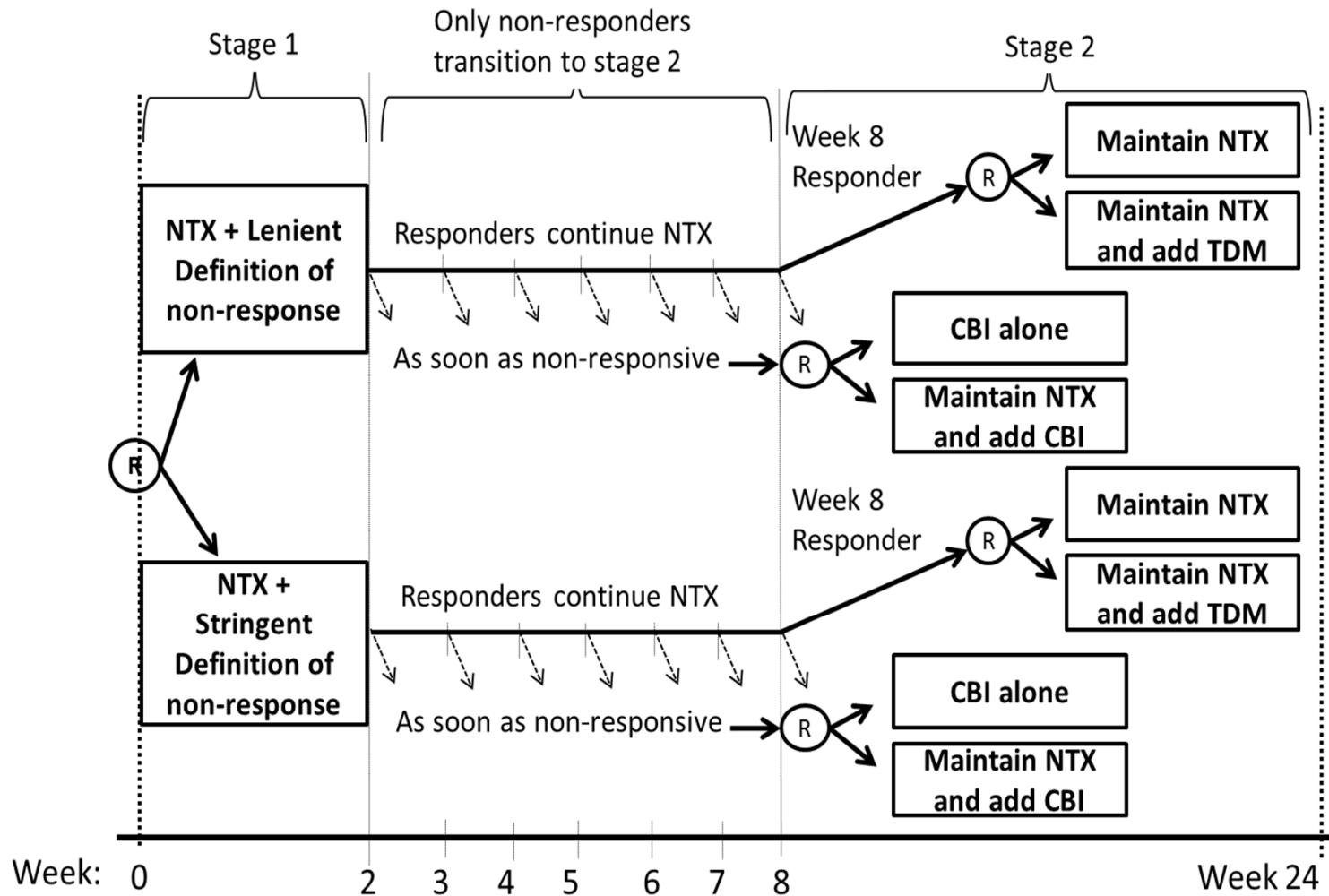


PI Amy Kilbourne

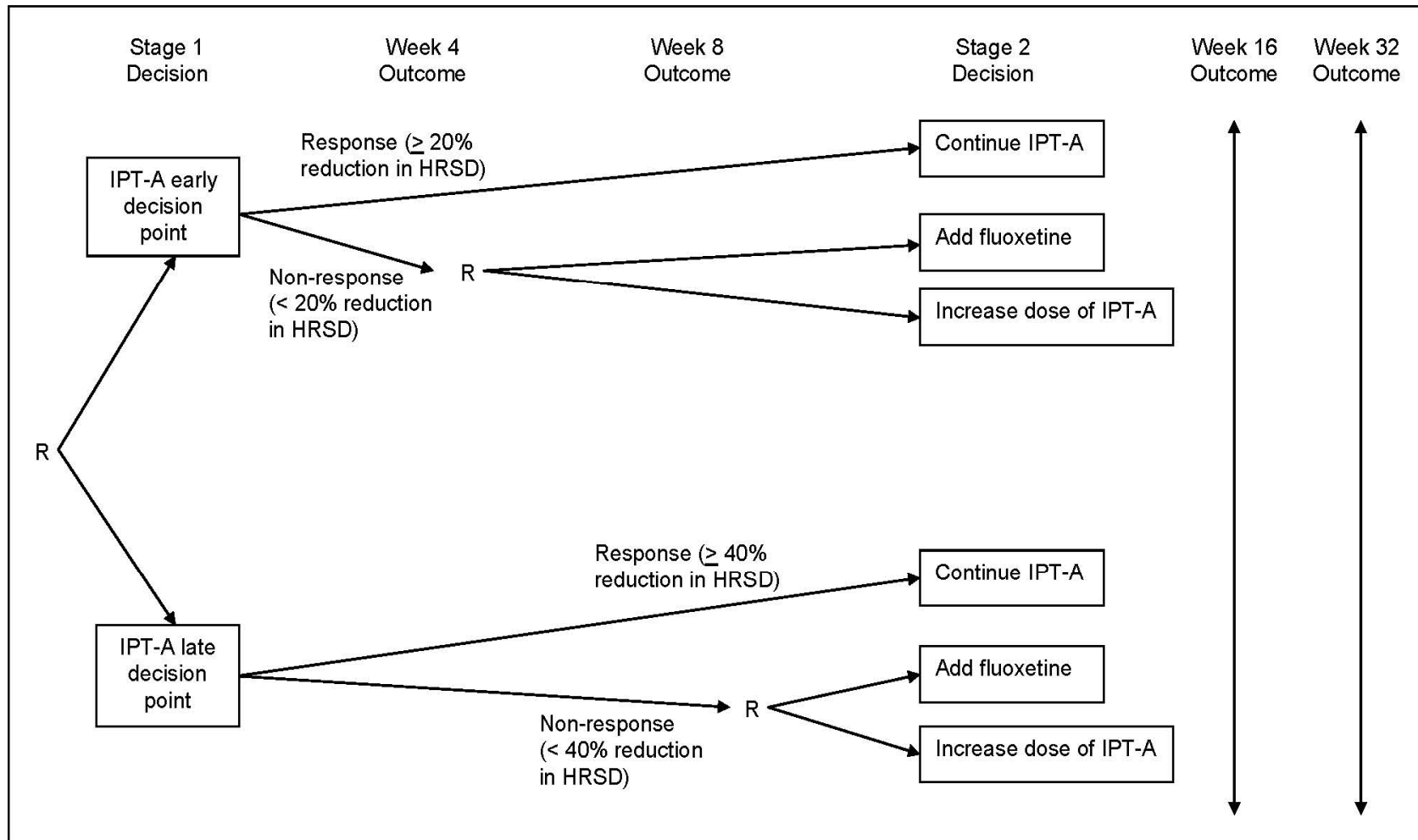
Kasari Autism Study



Oslin ExTEND study

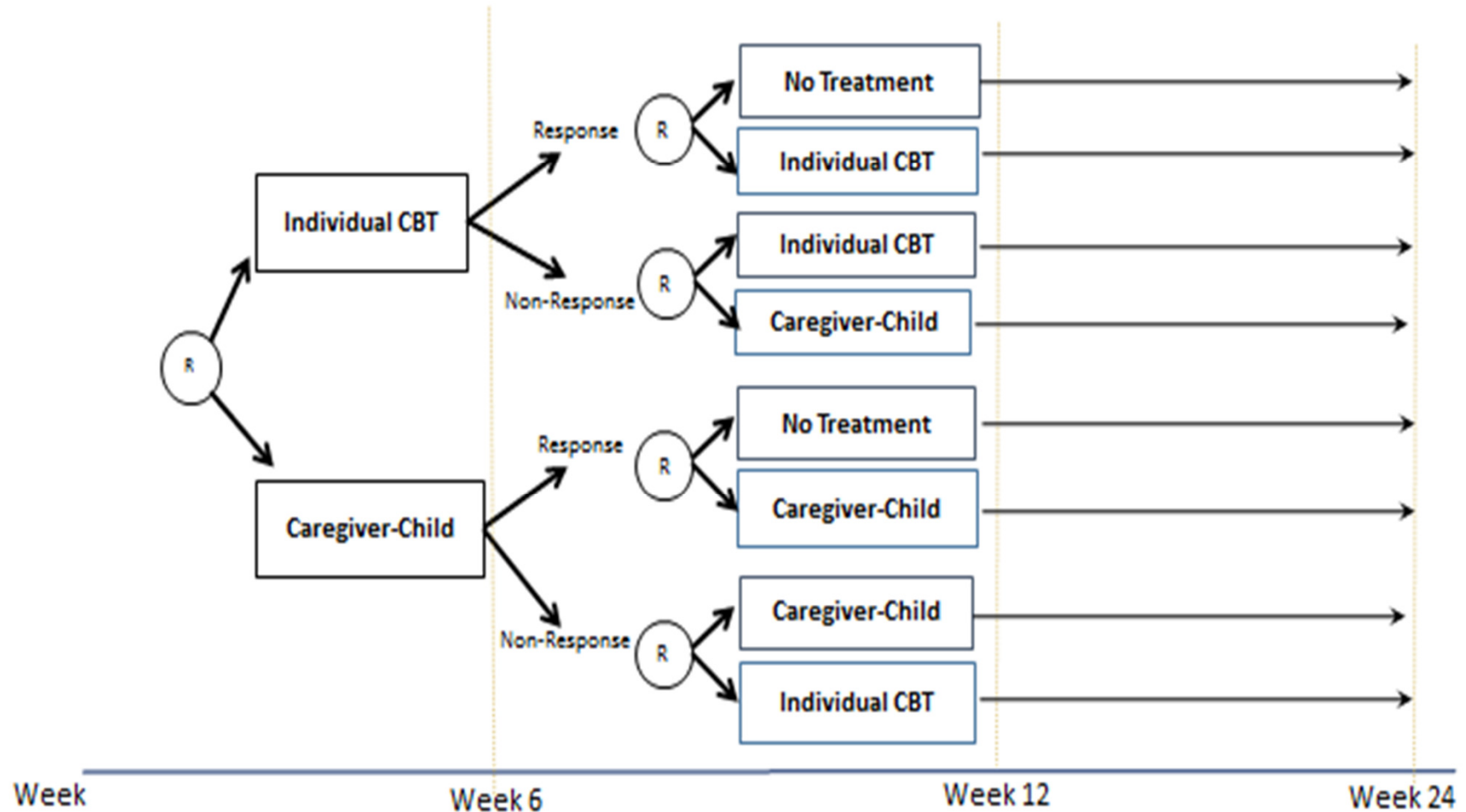


SMART for Adolescent Depression



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

SMART for Child Depression



PI: Dikla Eckshtain, Harvard University (NIMH K23)

Kasari Autism Study

