Sequential, Multiple Assignment, Randomized Trials

Module 2

Getting SMART About Developing Individualized, Adaptive Health Interventions

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Survey Research Center
SRC

The Methodology Center

MICHIGAN
STATISTICS

Before We Begin...Throughout This Module, Keep in Mind the End-of-Module Practice Exercise and Discussion Question

Exercise: *Begin thinking about a SMART design in your research.*

Discussion Question: *What is the primary purpose of a SMART? How are SMARTs different from standard RCTs?*

Some Critical Questions in Adaptive Health Intervention 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 (experimental) data for addressing these questions.

Outline

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

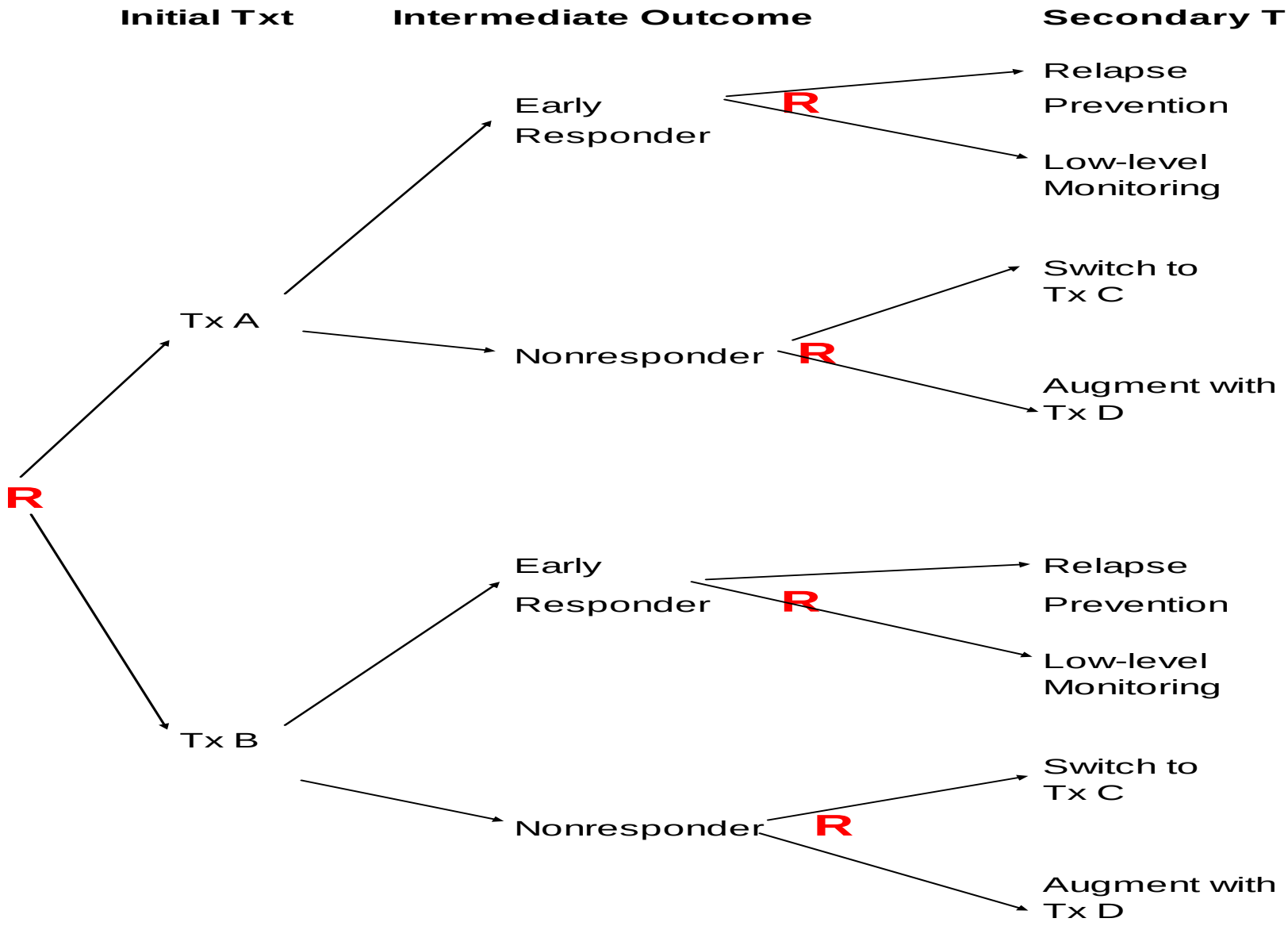
What is a SMART Study?

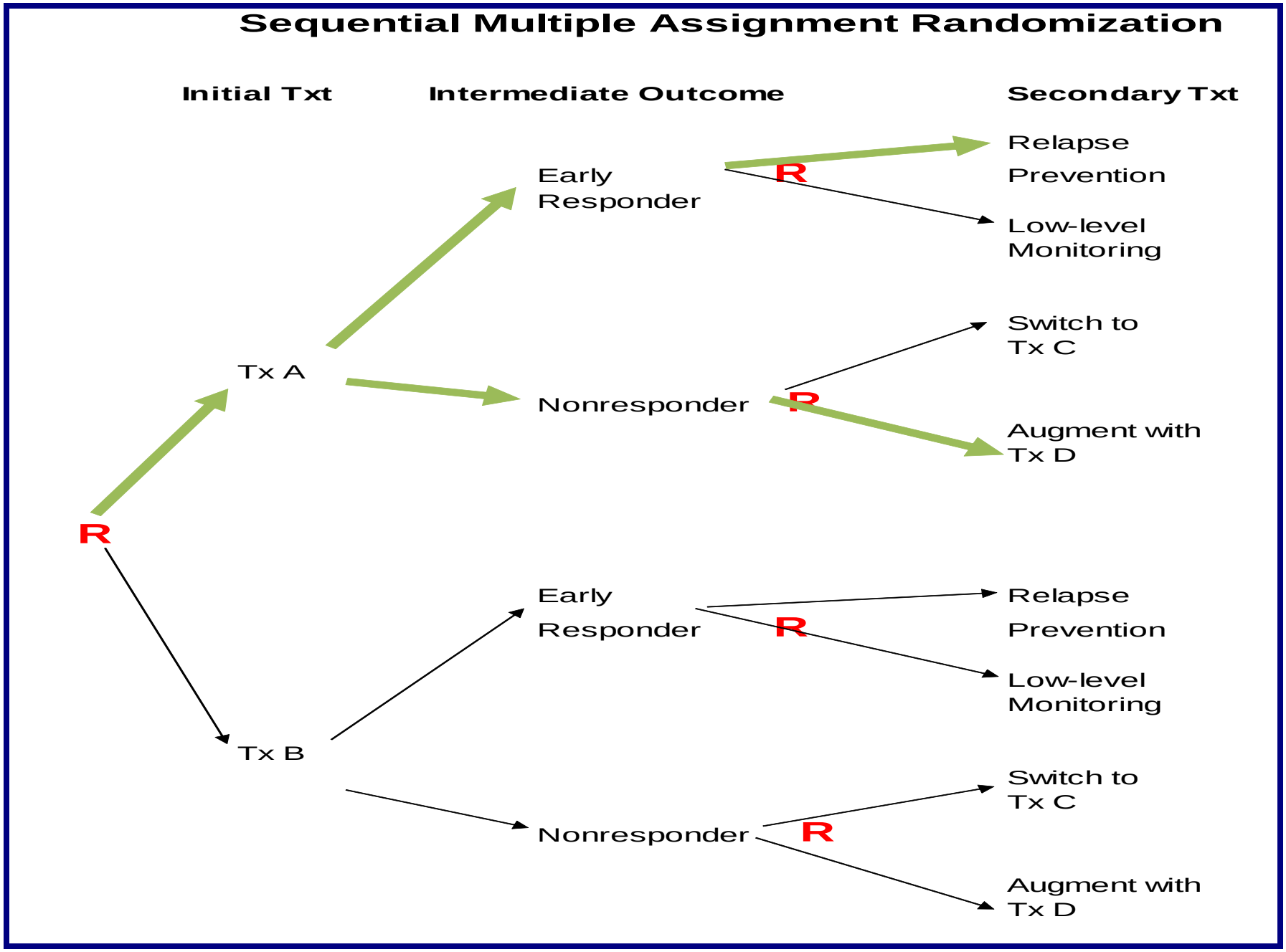
What is a sequential multiple assignment randomized trial (SMART)?

These are multi-stage trials; each stage corresponds to a critical treatment decision and a randomization takes place at each critical decision.

Goal is to inform the construction of adaptive health interventions.

Sequential Multiple Assignment Randomization




Sequential Multiple Assignment Randomization
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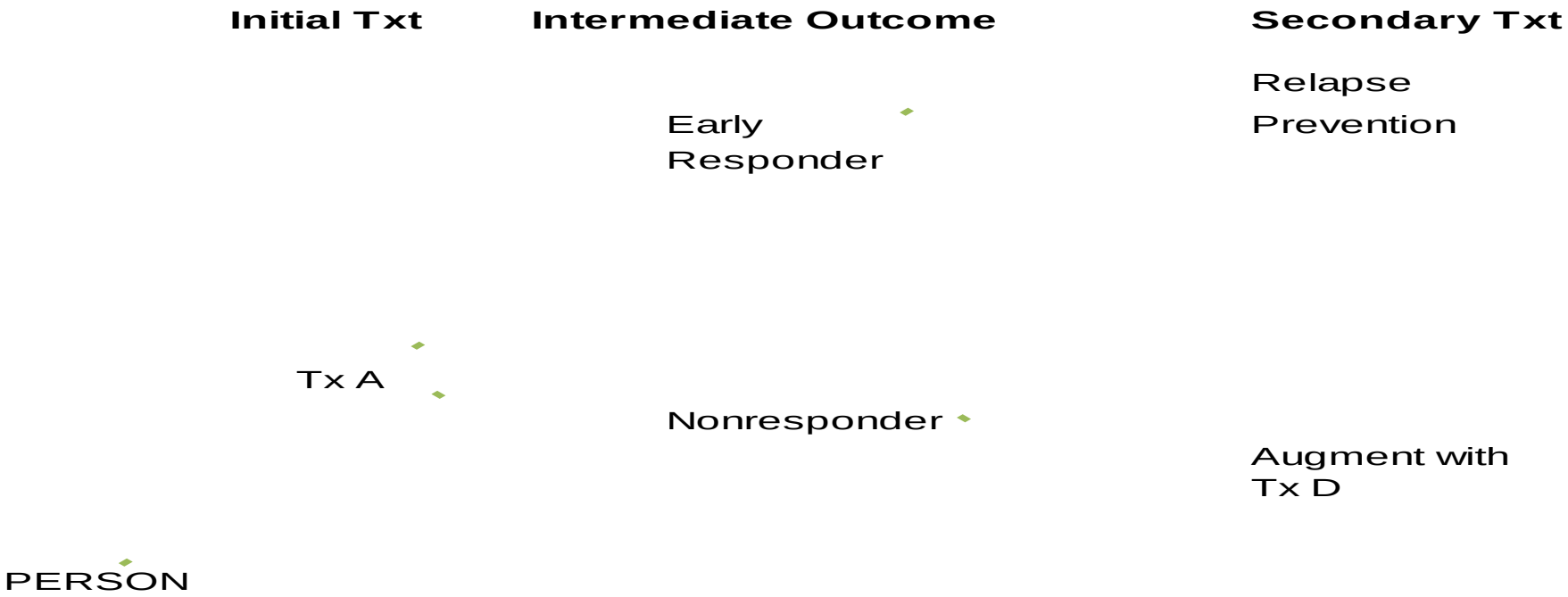
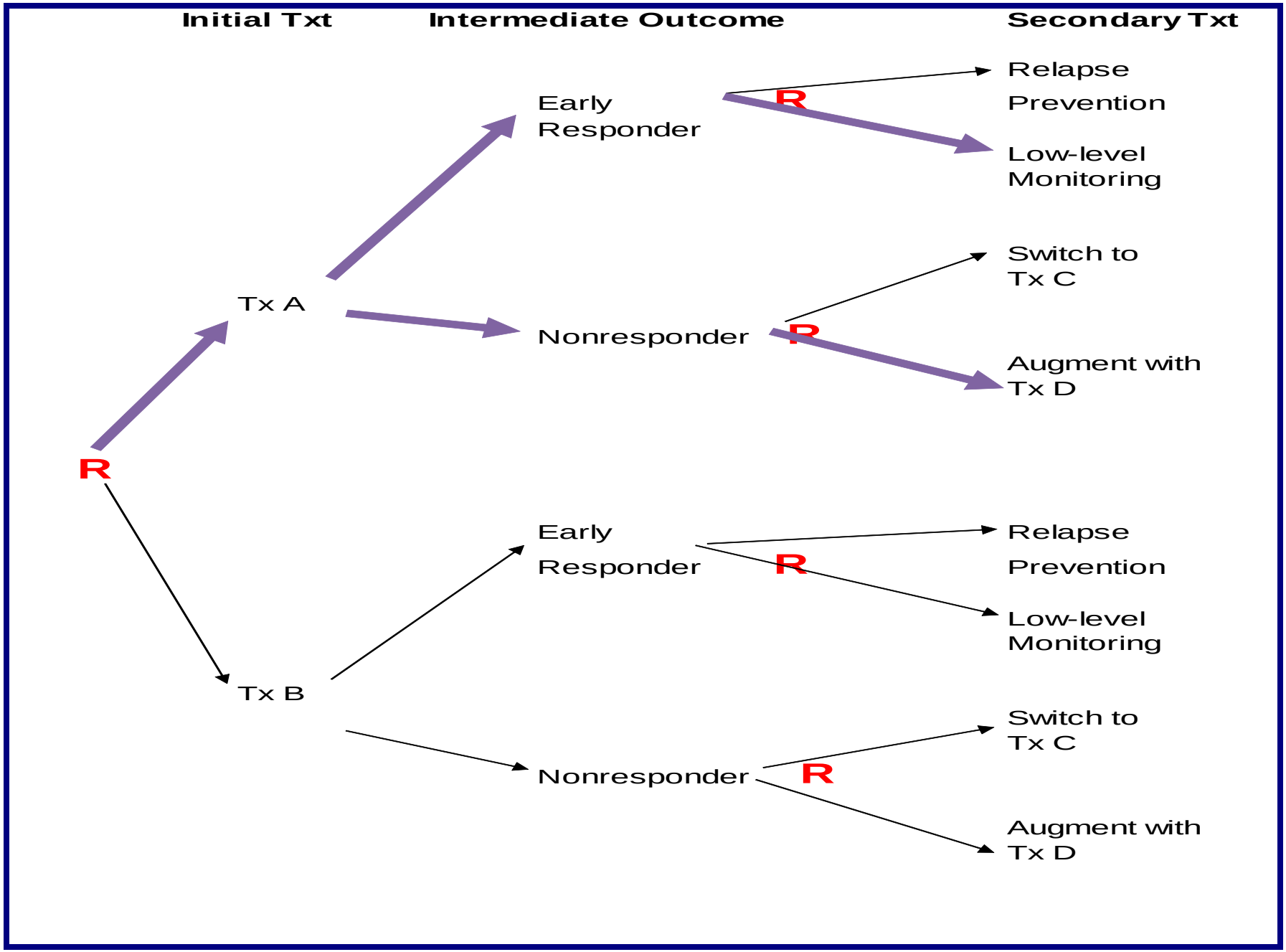


This is an example of one embedded adaptive health intervention. (Note: It has nothing to do with randomization.)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Challenges in constructing Adaptive Health Interventions

- Delayed, Prescriptive & Sample Selection Effects

  ---*sequential multiple assignment randomized trials (SMART)*

- Adaptive Health Interventions are Multi-component Treatments

  ---*series of screening/refining randomized trials prior to confirmatory trial (MOST).*

Alternate Approach I to Constructing an Adaptive Health Intervention

- Why not use data from multiple trials to construct the adaptive health 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 second, separate randomized trial of secondary treatments.

Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive health 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 health 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.

A Consequence of Delayed Therapeutic Effects

- Comparisons of initial treatments based on a acute 3 month outcome may result in a different result from a comparison of these two initial treatments based on a 6 month outcome.
- Restricting to 6 month outcomes, a comparison of initial treatments in months 0-3 followed by usual care in months 4-6 may differ from a comparison of initial treatments followed by one of several maintenance therapies in months 4-6.

Harnessing Delayed Therapeutic Effects

- Our goal is to ensure that the subsequent treatment builds on gains achieved by prior treatments even when the participant initially appears non-responsive.
- We want large positive delayed effects (i.e. large positive cross-over effects are great!)
- We want to prevent negative delayed effects.

Harnessing Delayed Therapeutic Effects

Using data from multiple trials to construct the adaptive health intervention is less helpful in harnessing delayed therapeutic effects because we would like to assess the combined effect of a sequence of treatments.

Prescriptive Effects

Why not use data from multiple trials to construct the adaptive health 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 health 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.

A Different Example of Sample Selection Effects

A scientist who has experience conducting non-responder trials comparing treatment A versus B decides to conduct a SMART. The scientist reports that when conducting the SMART he discovers that a large fraction of the non-responders do not want to be randomized to either treatment A or B.

What has happened?

Summary:

- When evaluating and comparing initial treatments, *in a sequence of treatments*, we need to take into account the effects of the secondary treatments, thus SMART

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

Alternate Approach II to Constructing an Adaptive Health Intervention

- Theory, clinical experience and expert opinion are critical in the development of adaptive health interventions!
- However, why not use theory, clinical experience and expert opinion to completely construct the adaptive health intervention and then compare this strategy against an appropriate alternative in a confirmatory randomized two group trial?

Why constructing an adaptive health intervention and then comparing the strategy against a standard alternative is not always the answer.

- Don’t know why your adaptive health intervention worked or did not work. Did not open black box.
- We don’t know what components of the adaptive health intervention are (in)active. Is the first stage treatment or the second treatment or the tactical decisions regarding the criterion for nonresponse or the timing of assessment of nonresponse sequence effective?

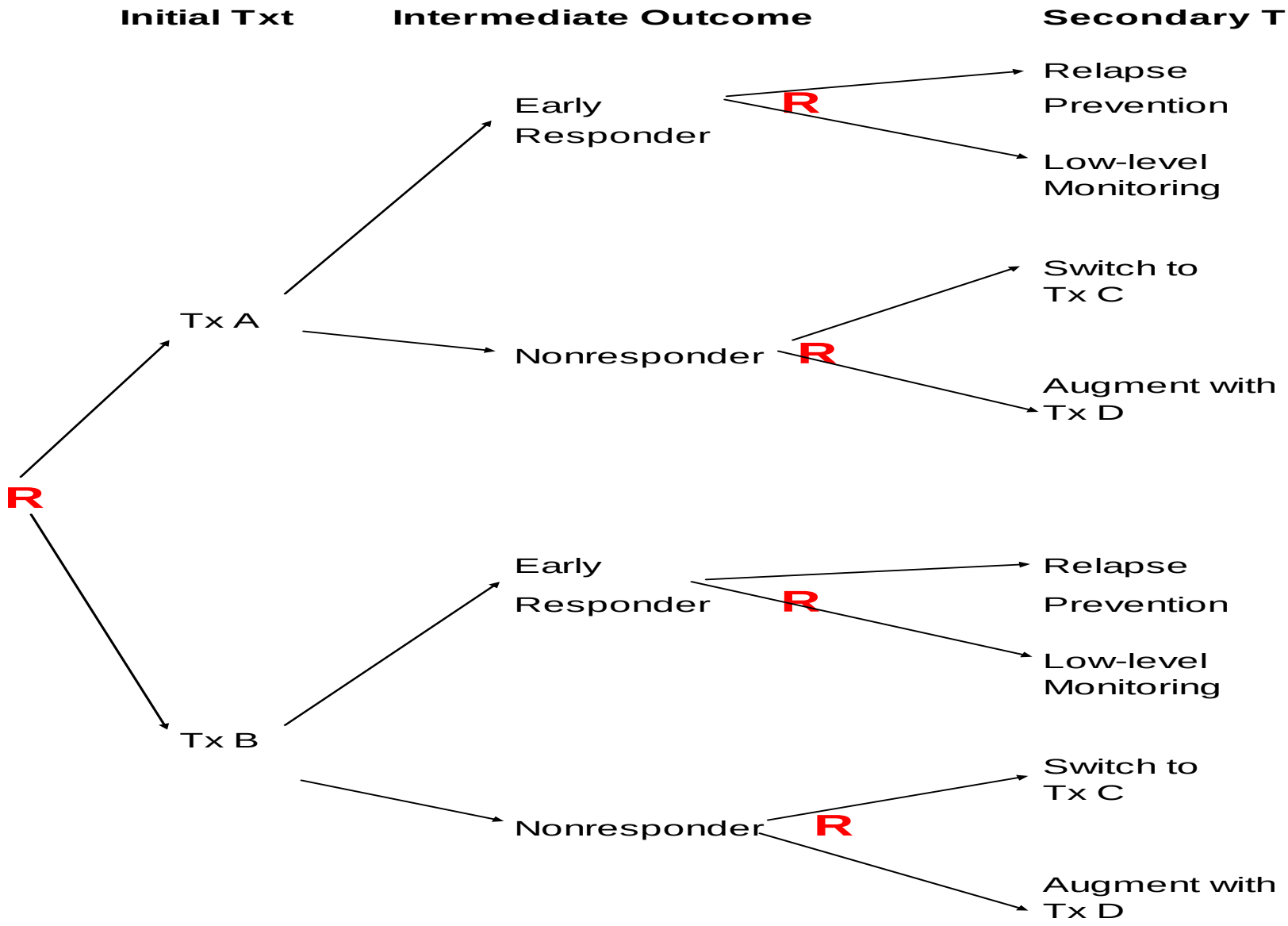
Meeting the Challenges

Delayed/Prescriptive/Sample Selection Effects: SMART

Developing Multi-Component Interventions: Screening/refining randomized trials prior to a confirmatory trial (MOST).

The SMART design is one of the screening/refining randomized trials in MOST

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 (2: primary analysis & in field) Tx of Autism
- McKay (in field) Treatment of Alcohol and Cocaine Dependence

Outline

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Critical Decisions

- Choose two or three critical decisions to address.

- Examples of critical decisions
  - Sequencing decisions: Which treatment to try first? Which treatment to try if individual shows signs of nonresponse? Which treatment to try if the individual is doing well?
  - Timing decisions: How soon do we declare nonresponse? How soon do we declare response?

- Which decisions are most controversial or need investigation? Which decisions are likely to have the biggest impact on the outcome?

Critical Decisions

•In planning the study of Naltrexone for alcohol dependence, we realized that different researchers and clinicians use different criteria for non-response ranging from at least 5 heavy drinking days to at least 2 heavy drinking days.

- •This timing decision became one of the critical decisions to investigate.

•Other critical decisions involved which maintenance treatment to provide responders and which treatment to provide nonresponders.

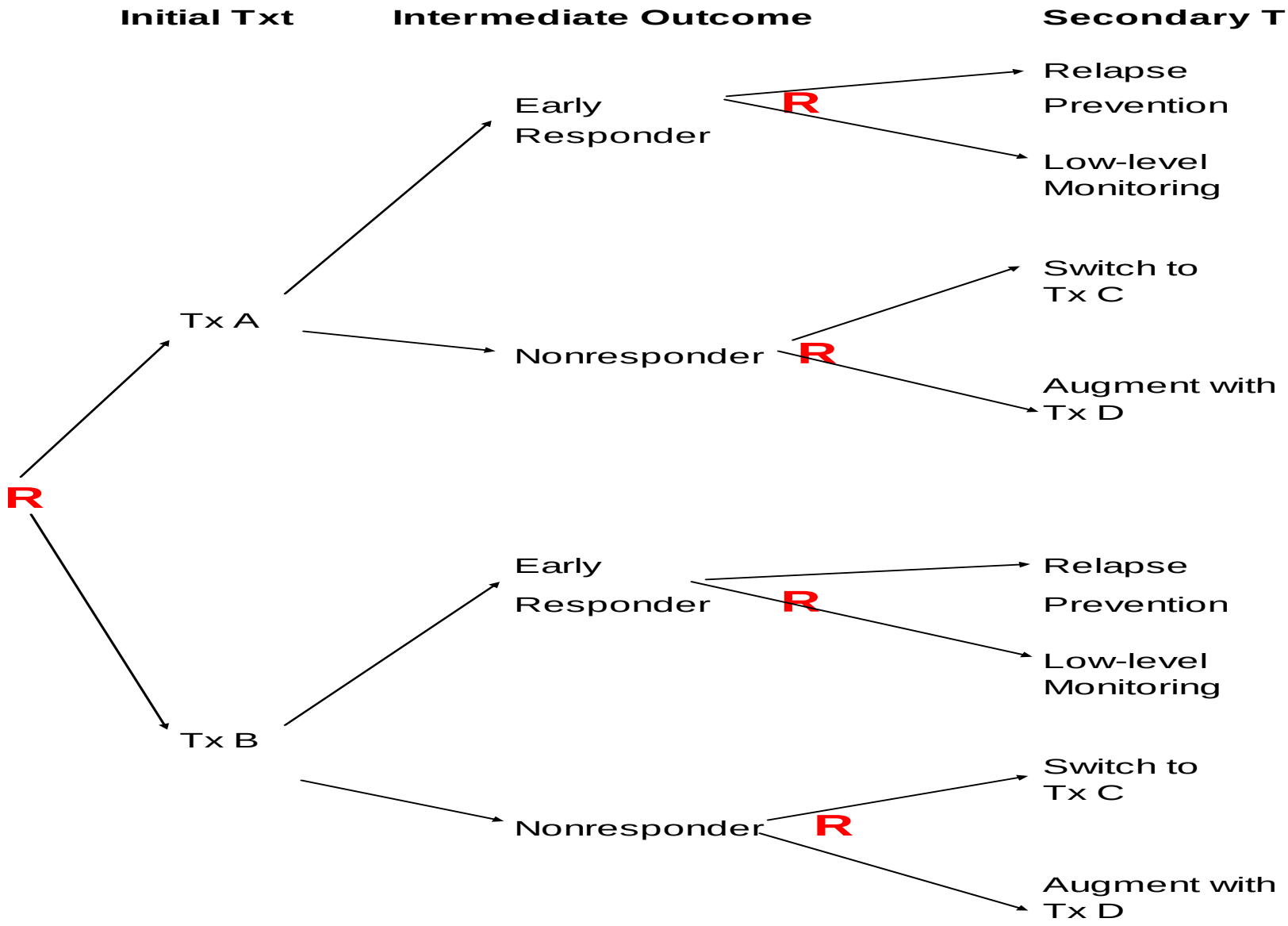
SMART Treatment Stages

•Each treatment stage (i.e., phase) in the SMART corresponds to a critical decision.

•We randomize participants at each treatment stage among different treatment options.

•The first stage of the alcohol dependence study involved randomization to either a "≥ 5 HDD nonresponse definition" or a "≥ 2 HDD nonresponse definition."

Sequential Multiple Assignment Randomization



SMART Design Principles

•KEEP IT SIMPLE: At each stage (critical decision point), restrict class of treatments only by clear 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 health intervention.

SMART Design Principles

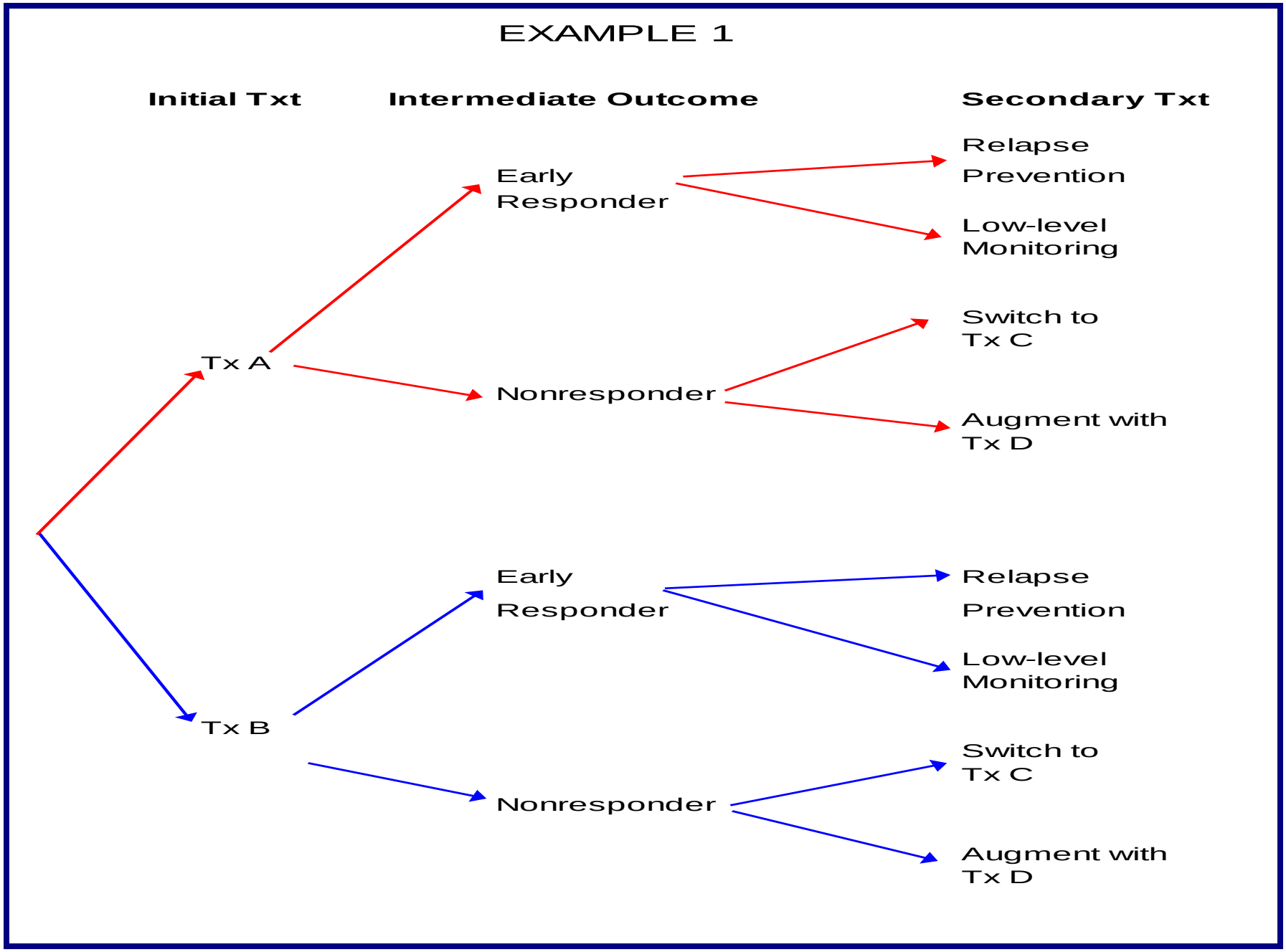
- Choose primary hypotheses that are both scientifically important on their own and also aid in developing the adaptive health intervention.
  - Power trial to address these hypotheses.

- Choose secondary hypotheses that further develop the adaptive health intervention and use the randomization to eliminate confounding.
  - Trial is not necessarily powered to address these hypotheses.

SMART Designing Principles: Primary Hypothesis

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

•EXAMPLE 2: (need larger *sample size*): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.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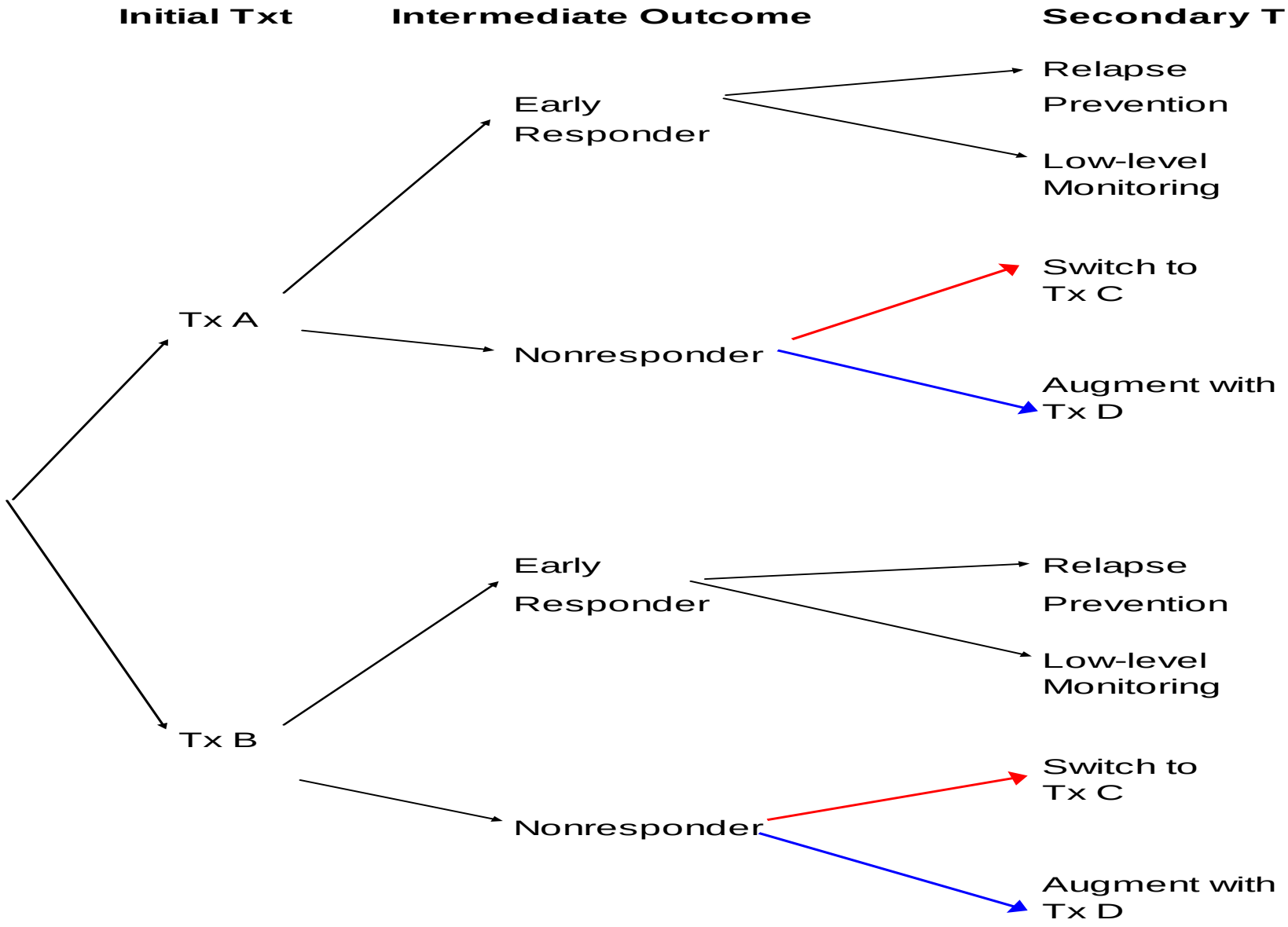
EXAMPLE 2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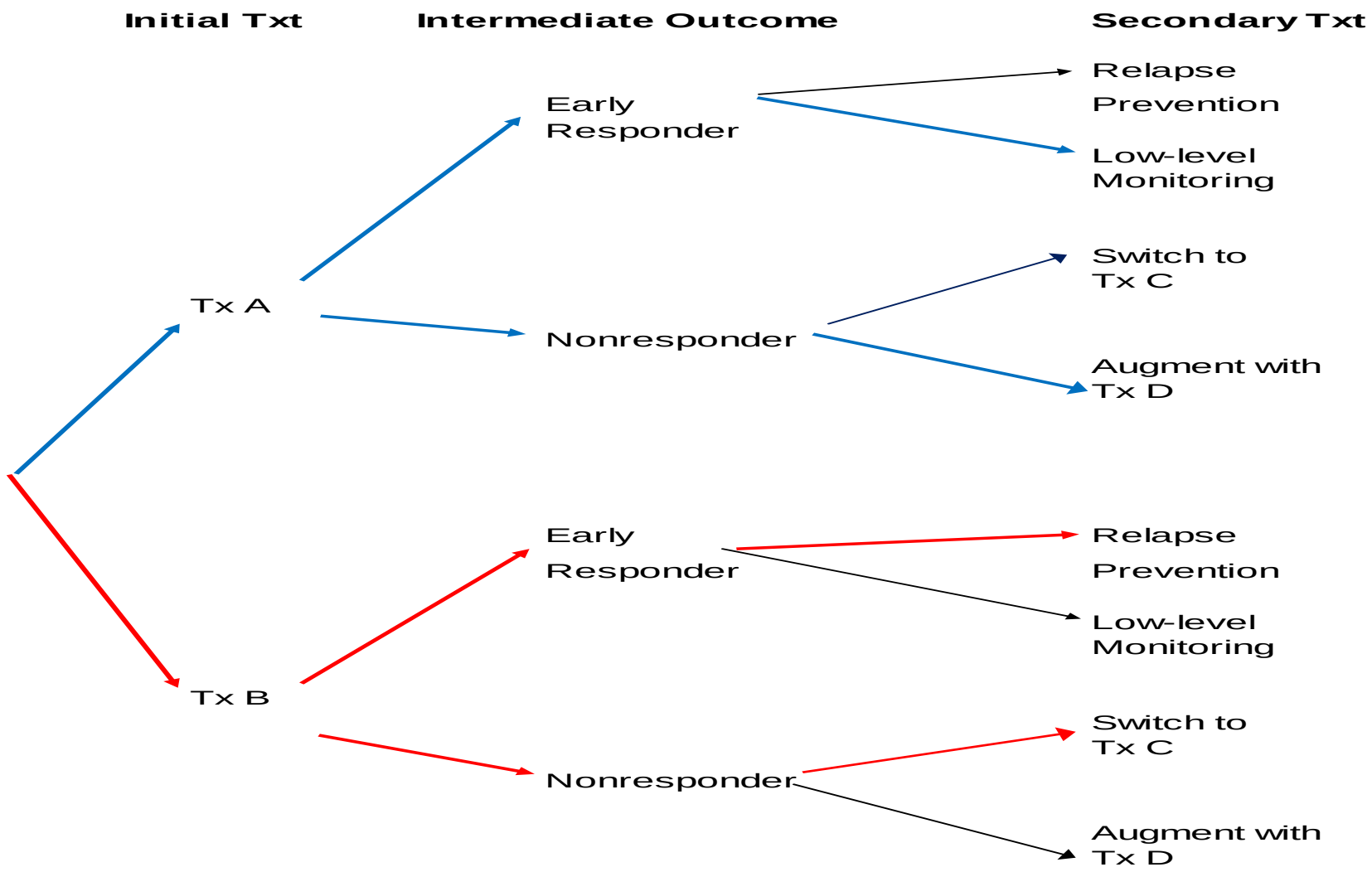
SMART Designing Principles: Primary Hypothesis

•EXAMPLE 3: (need larger *sample size*): Hypothesize that embedded adaptive health intervention 1 (in blue) results in improved symptoms as compared to embedded adaptive health intervention 2 (in red)

EXAMPLE 2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SMART Designing Principles: Sample Size Formula

- EXAMPLE 1: (need smaller sample size): 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: (need larger sample size): 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.*

Example 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

An analysis that is less useful in the development of adaptive health interventions:

Decide whether treatment A is better than treatment B by comparing proportion of early responders.

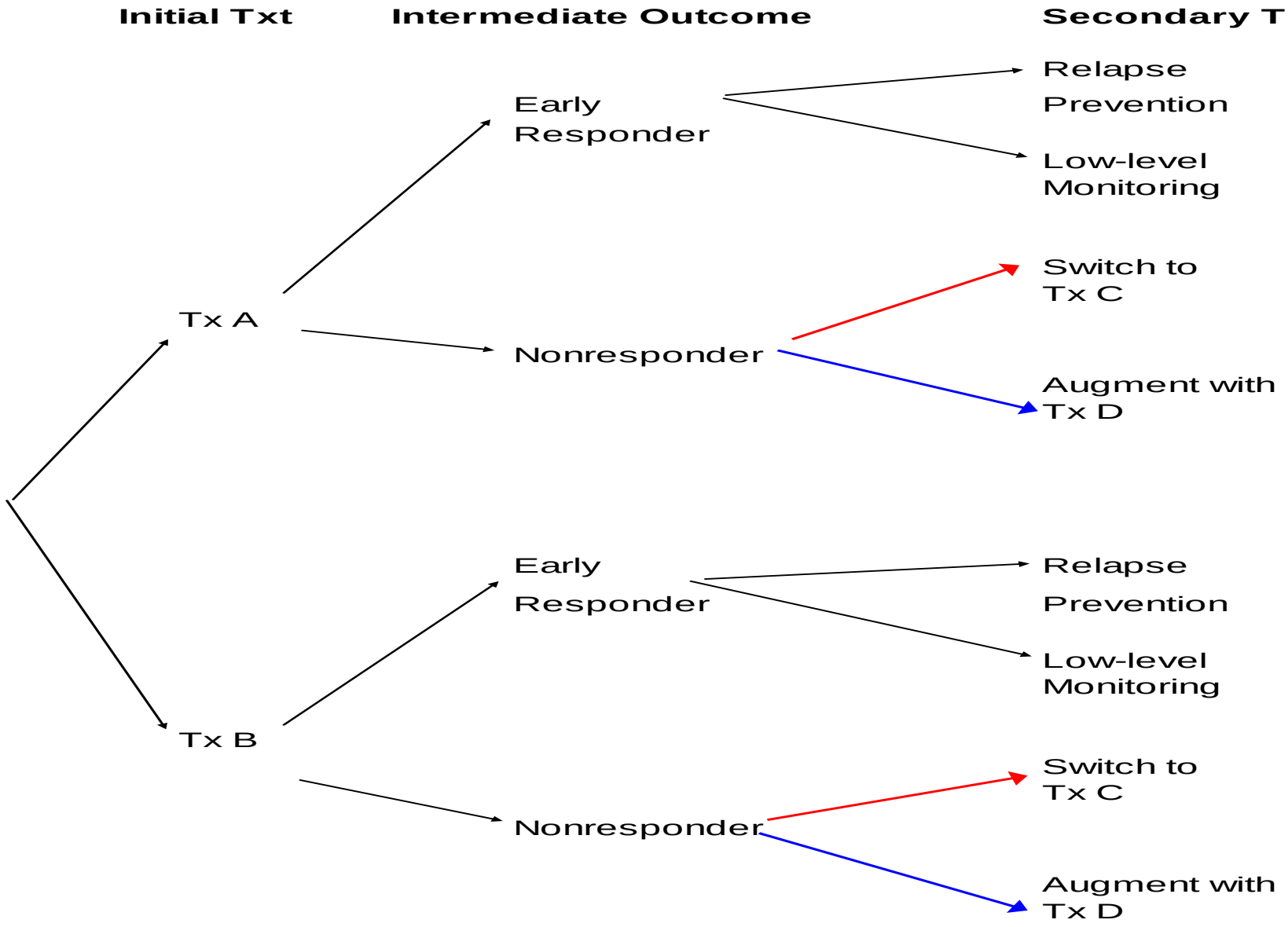
Interesting, but not useful in building an AHI.
Also, responder status not an outcome---part of treatment.

SMART Designing Principles

•Choose secondary hypotheses that further develop the adaptive health intervention 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).

EXAMPLE 2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Summary & Discussion

- We have a sample size formula that specifies the sample size necessary to detect an embedded adaptive health intervention that results in a mean outcome δ standard deviations better than the other embedded adaptive health interventions 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

Practice Exercise and Discussion Question

Exercise: *Begin thinking about a SMART design in your research. What would the first randomization be? The second randomization? How can you incorporate the AHI you developed in Module 1 into this design?*

Discussion Question: *What is the primary purpose of a SMART? How are SMARTs different from standard RCTs?*

Questions?

More information

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

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