Outline

- Why Adaptive Treatment Strategies?
- Why SMART experimental designs?
- Design Principles and Analysis
- Discussion

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Adaptive Treatment Strategies are individually tailored treatments, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

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Why Adaptive Treatment Strategies?

- 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
- Improvement often marred by relapse
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
- Co-occurring disorders may be common

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Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

- Treatment incurs side effects and substantial burden, particularly over longer time periods.
- Problems with adherence:
  - Variations of treatment or different delivery mechanisms may increase adherence
  - Excessive treatment may lead to non-adherence
- Treatment is costly (Would like to devote additional resources to patients with more severe problems)

More is not always better!

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Example of an Adaptive Treatment Strategy

Drug Court Program for drug abusing offenders. Goal is to minimize recidivism and drug use.

High risk offenders are provided biweekly court hearings; low risk offenders are provided "as-needed court hearings." In either case the offender is provided standard drug counseling. If the offender becomes non-responsive then intensive case management along with assessment and referral for adjunctive services is provided. If the offender becomes noncompliant during the program, the offender is subject to a court determined disposition.

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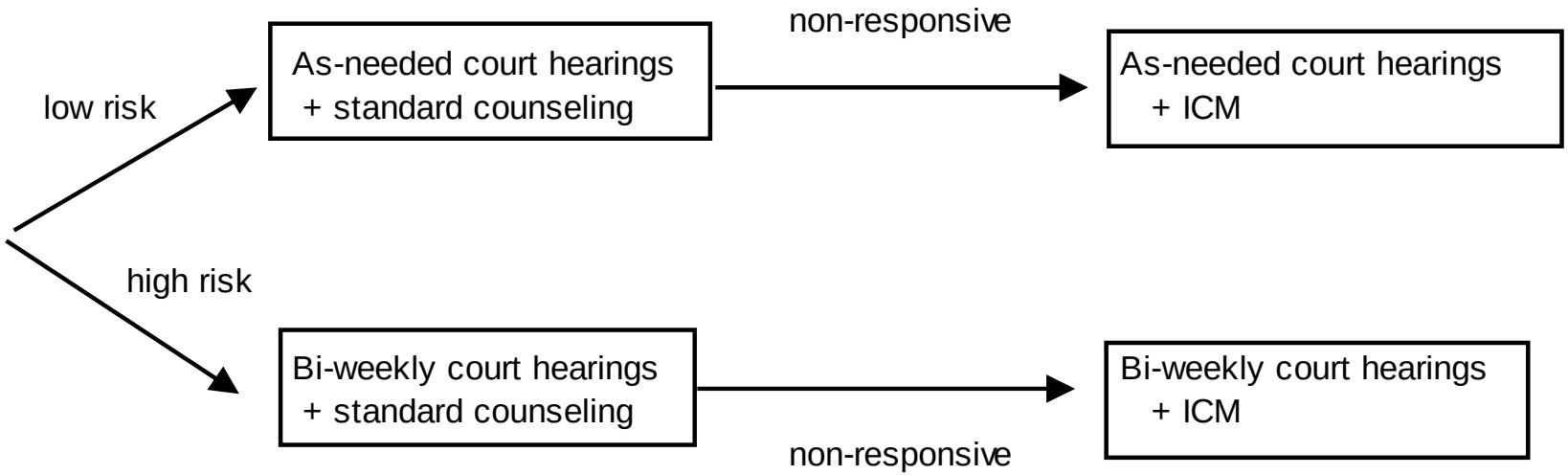
Hypothetical Adaptive Drug Court Program



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?

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Why SMART Trials?

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

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

Goal is to inform the construction of an adaptive treatment strategies.

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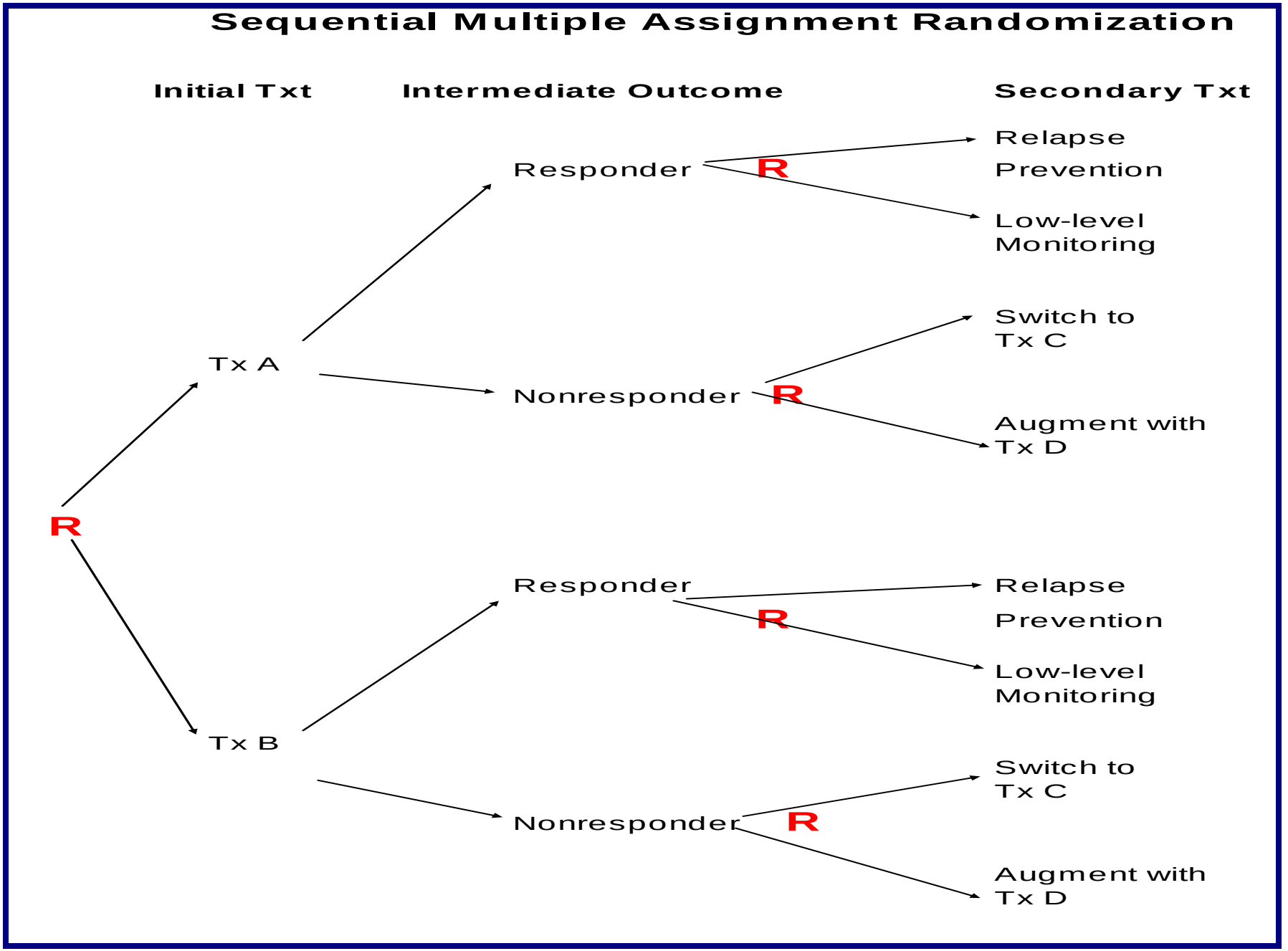
Sequential Multiple Assignment Randomization
Initial Txt
Intermediate Outcome
Secondary Txt
R
Tx A
Tx B
Responder
Nonresponder
Responder
Nonresponder
R
R
R
R
Relapse Prevention
Low-level Monitoring
Switch to Tx C
Augment with Tx D
Relapse Prevention
Low-level Monitoring
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First Alternate Approach

- Why not use data from multiple trials to construct the adaptive treatment strategy?

  • 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

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.

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Delayed Therapeutic Effects

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

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Diagnostic Effects

Initial 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.

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Cohort Effects

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.

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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 randomized trials may yield information about different populations from SMART trials.

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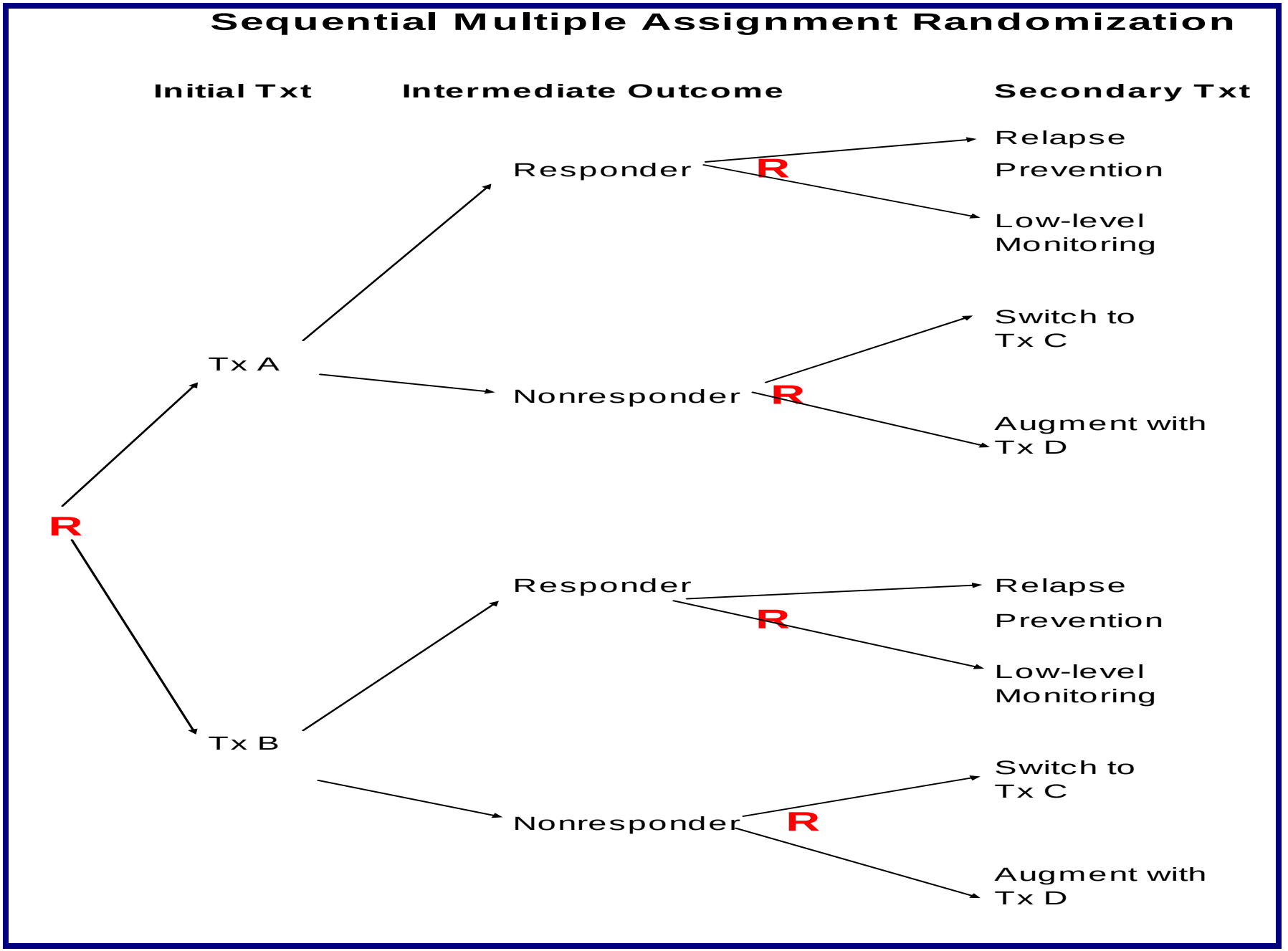
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Examples of "SMART" designs:

- CATIE (2001) Treatment of Psychosis in Alzheimer's Patients
- CATIE (2001) Treatment of Psychosis in Schizophrenia
- STAR*D (2003) Treatment of Depression
- Pelham (on-going) Treatment of ADHD
- Oslin (on-going) Treatment of Alcohol Dependence

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SMART Designing Principles

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SMART Designing Principles

•KEEP IT SIMPLE: At each stage, restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (time until nonresponse, adherence, burden, stress level, 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 treatment strategy.

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SMART Designing Principles

Choose primary hypotheses that are both scientifically important and aid in developing the adaptive treatment strategy.

- Power trial to address these hypotheses.

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SMART Designing Principles: Primary Hypothesis

- 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.

- 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.

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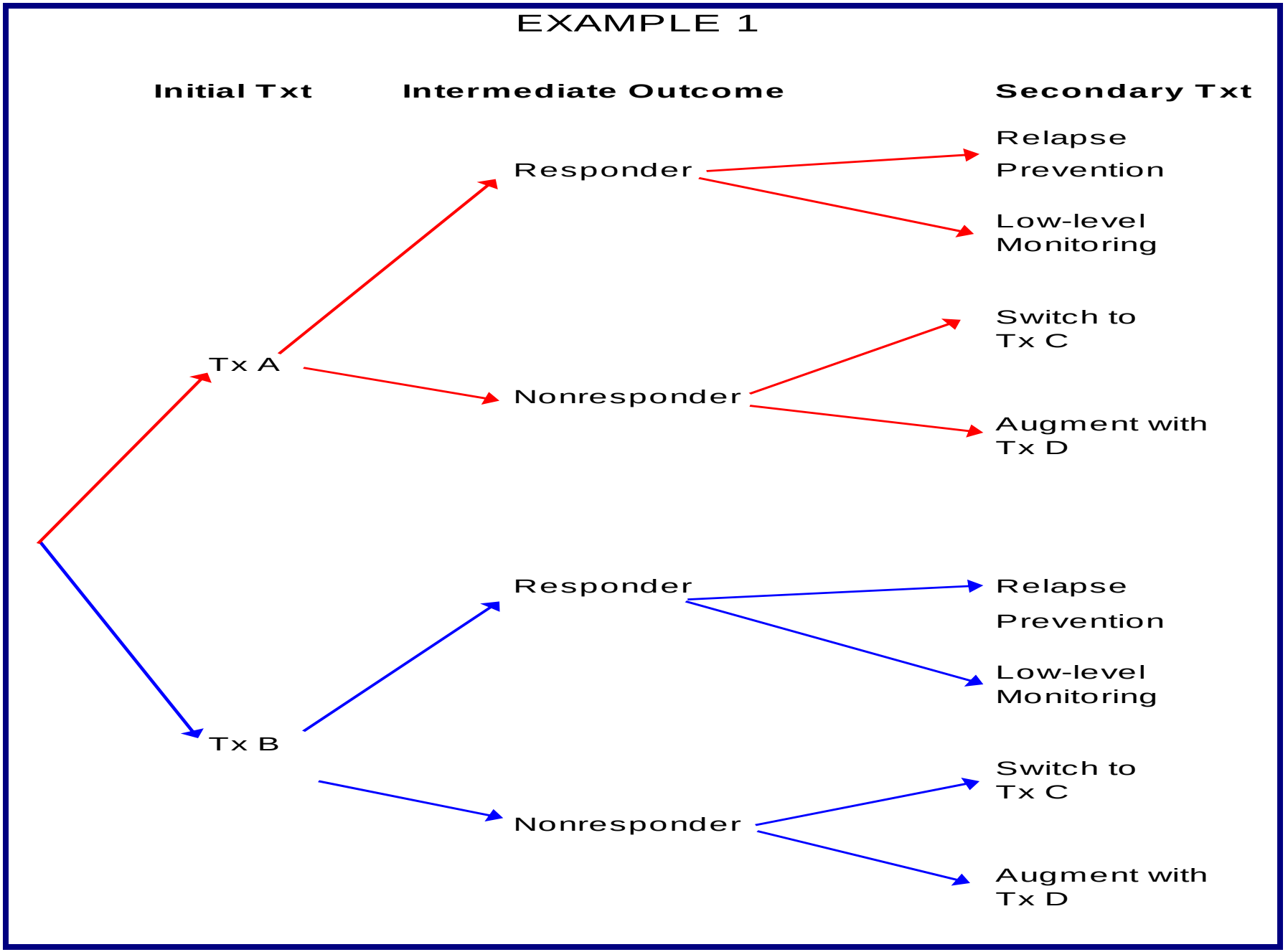
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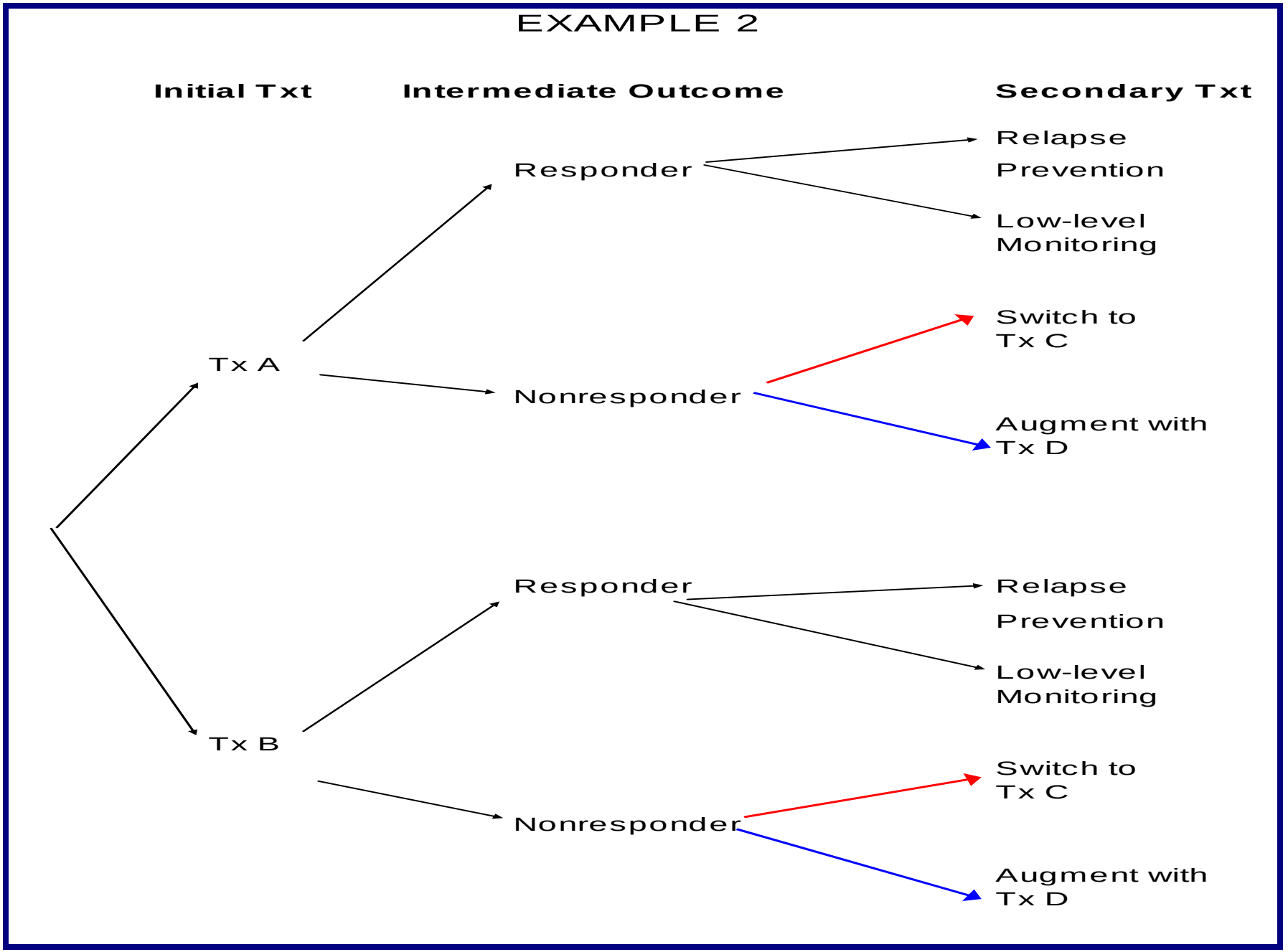
EXAMPLE 2
Initial Txt
Intermediate Outcome
Secondary Txt
Tx A
Responder
Relapse Prevention
Low-level Monitoring
Nonresponder
Switch to Tx C
Augment with Tx D
Tx B
Responder
Relapse Prevention
Low-level Monitoring
Nonresponder
Switch to Tx C
Augment with Tx D

An analysis that is less useful in the development of adaptive treatment strategies:

Decide whether treatment A is better than treatment B by comparing intermediate outcomes (proportion of immediate responders).

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.*

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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

$\alpha = .05$, power $= 1 - \beta = .85$

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SMART Designing Principles

•Choose secondary hypotheses that further develop the adaptive treatment strategy 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 (augment D is motivational interviewing).

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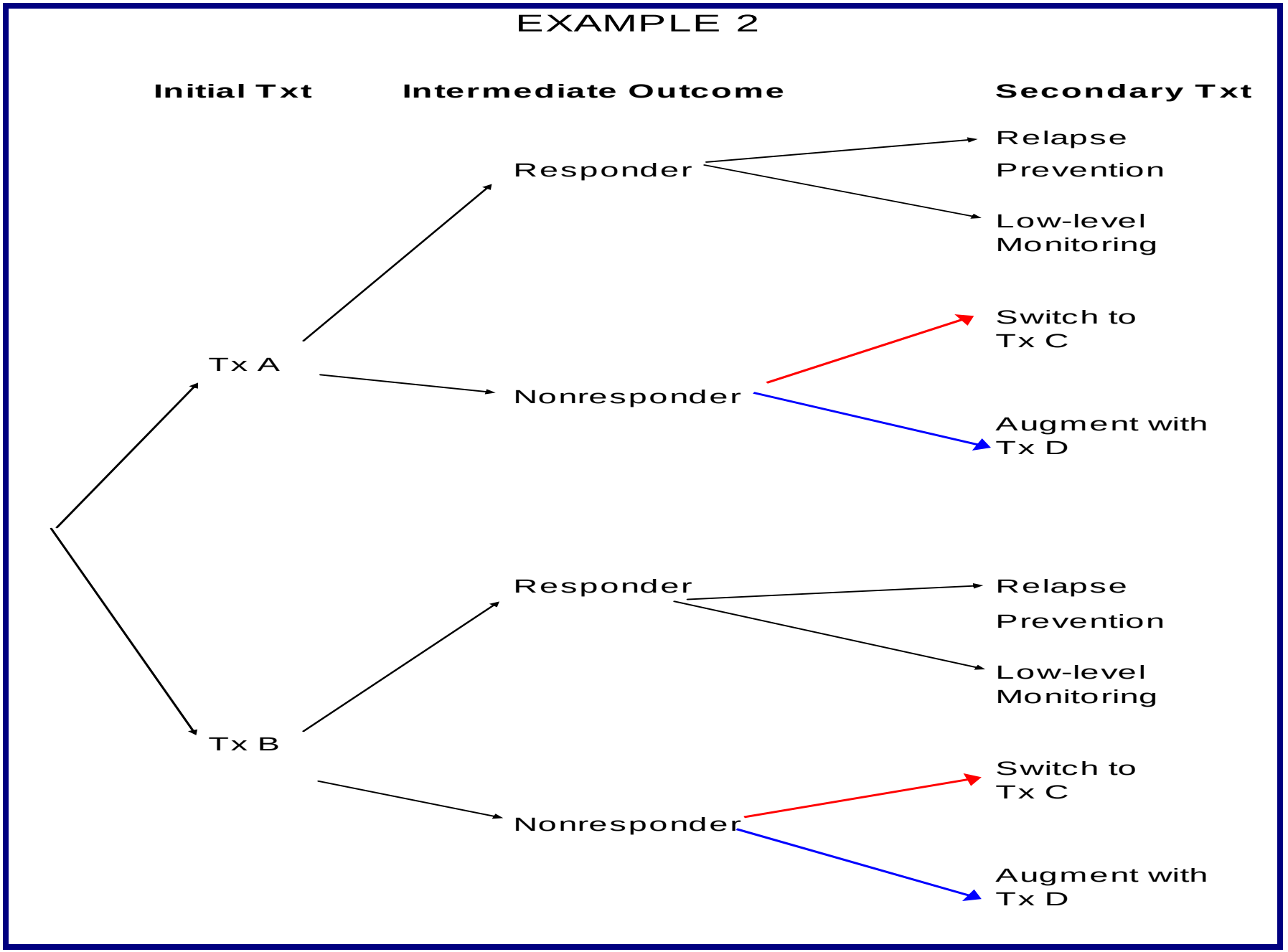
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Discussion

Secondary analyses can use pretreatment variables and outcomes to provide evidence for a more sophisticated adaptive treatment strategy. (when and for whom?)

- We are working on a sample size formula that allows us to ask the question: "What sample size do I need so as to detect an adaptive treatment strategy that results in a mean outcome δ standard deviations better than the other strategies with 90% probability?"
- SMART design and analyses targeted at scientific goal of informing the construction of a high quality adaptive treatment strategy
- Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.

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Discussion

- Industry should be interested in the SMART design because:
  - For some individuals the treatment may require an adjunctive therapy—when should this therapy be provided and to whom should this therapy be provided?
  - Some treatments may be most useful when considered as part of a sequence of treatments (e.g. a treatment may not be effective for all but has low side effects/is inexpensive and when it is not effective, patient responses provide an indication of which treatment should be used next.)

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This seminar can be found at:

http://www.stat.lsa.umich.edu/~samurphy/seminars/ISCTM07.ppt

This seminar is based partially on papers with K. Lynch, J. McKay, D. Oslin and T. Ten Have, A. J. Rush, J. Pineau and L. Collins. Email me with questions or if you would like a copy:

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