SMART design: Introduction and Novel use in Rare Diseases

ISCB in Vigo, Spain

Kelley Kidwell

Department of Biostatistics, University of Michigan

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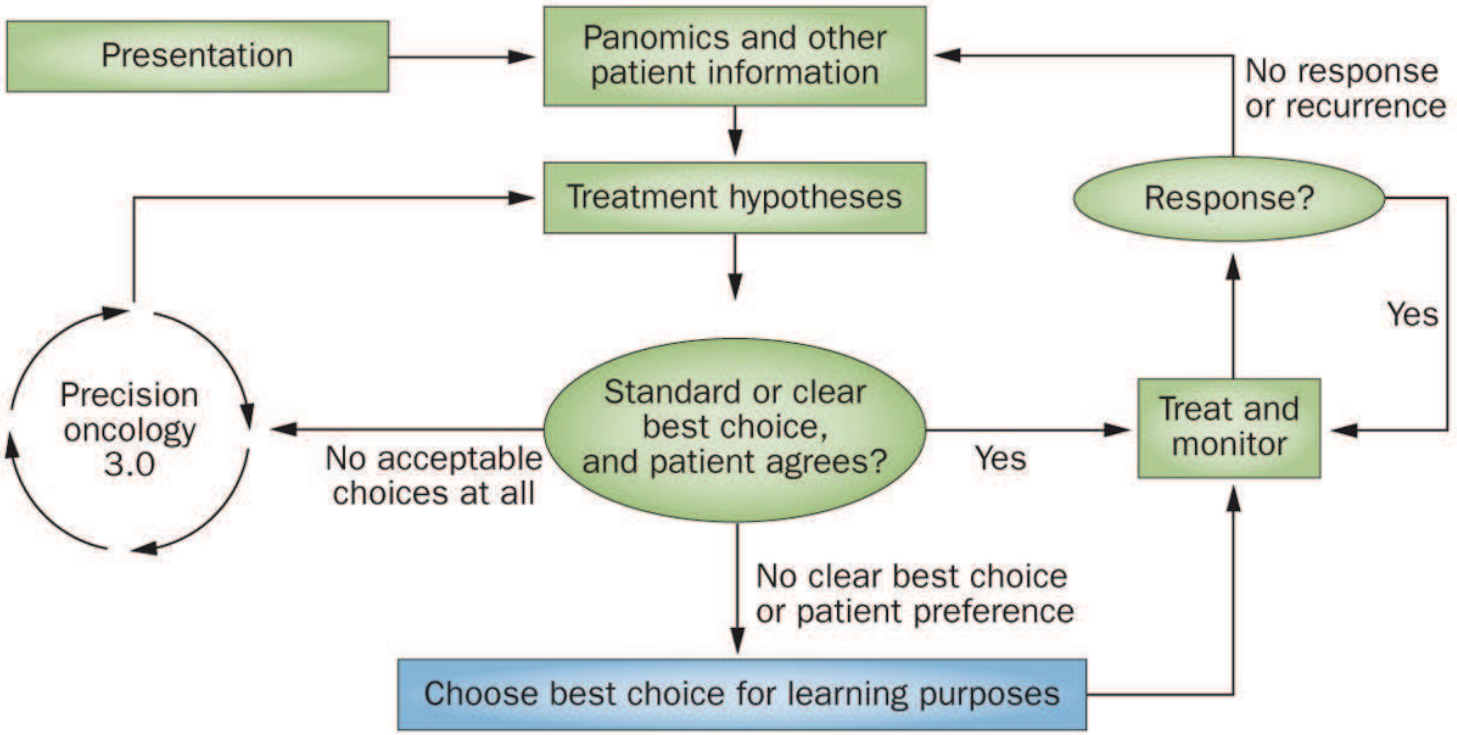
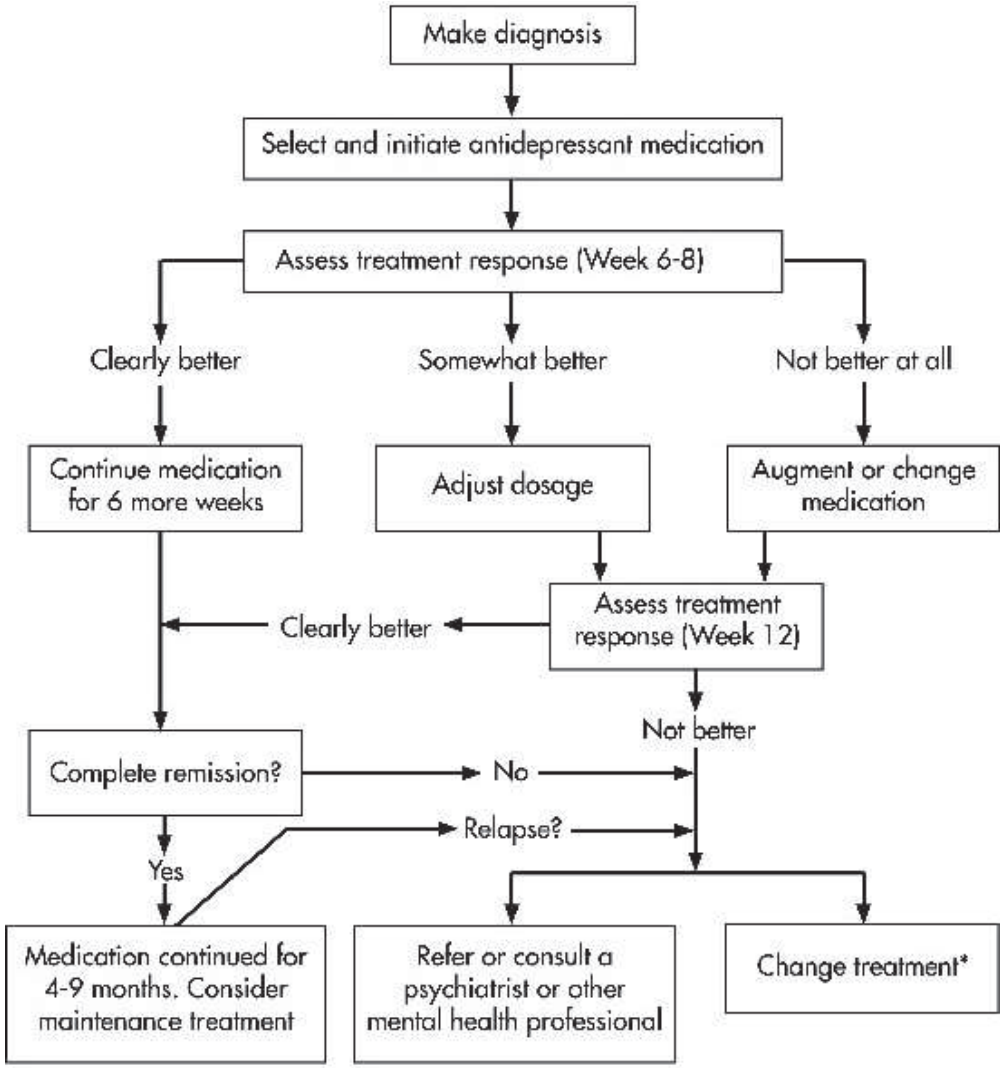
Cancer



Shrager, J. & Tenenbaum, J. M. (2014) Rapid learning for precision oncology *Nat. Rev. Clin. Oncol.*

DEPRESSION



*Short-term behavior counseling has been shown to be just as effective as anti-depression medication

Dynamic Treatment Regimens

A DTR

- a.k.a. adaptive interventions, adaptive treatment strategies, stepped care, treatment policies
- is a sequence of **individually tailored treatments** that specify whether, how and/or when to alter the intensity, type, dose, or delivery of treatment at **critical decision points** in the course of care
- Operationalize sequential decision making with the aim of improving clinical practice

Dynamic treatment regimens

Example 1: Treatment of Leukemia

First receive standard chemotherapy. **If the patient responds** to chemotherapy and achieves remission, then receive maintenance treatment cytarabine; **if remission is not achieved**, there is no further treatment.

Example 2: Advanced Prostate Cancer

First receive combination chemotherapy paclitaxel + estramustine + etoposide (TEC). **If successful** (a decrease of 40% or more in PSA from baseline at diagnosis, with no evidence of disease progression at any site) at 8 weeks, then continue TEC; **otherwise** switch to cyclophosphamide + vincristine + dexamethasone (CVD).

Dynamic treatment regimens

- There are often **many questions that need to be answered to develop a good DTR**
  - What is the best first-line intervention?
  - What is the best measure of response to see if the intervention is successful?
  - When is the best time to measure response to the initial intervention?
  - Can those who do not respond to the initial intervention be rescued with further treatment? If so, is it best to switch treatment, add treatment, or intensify current treatment?

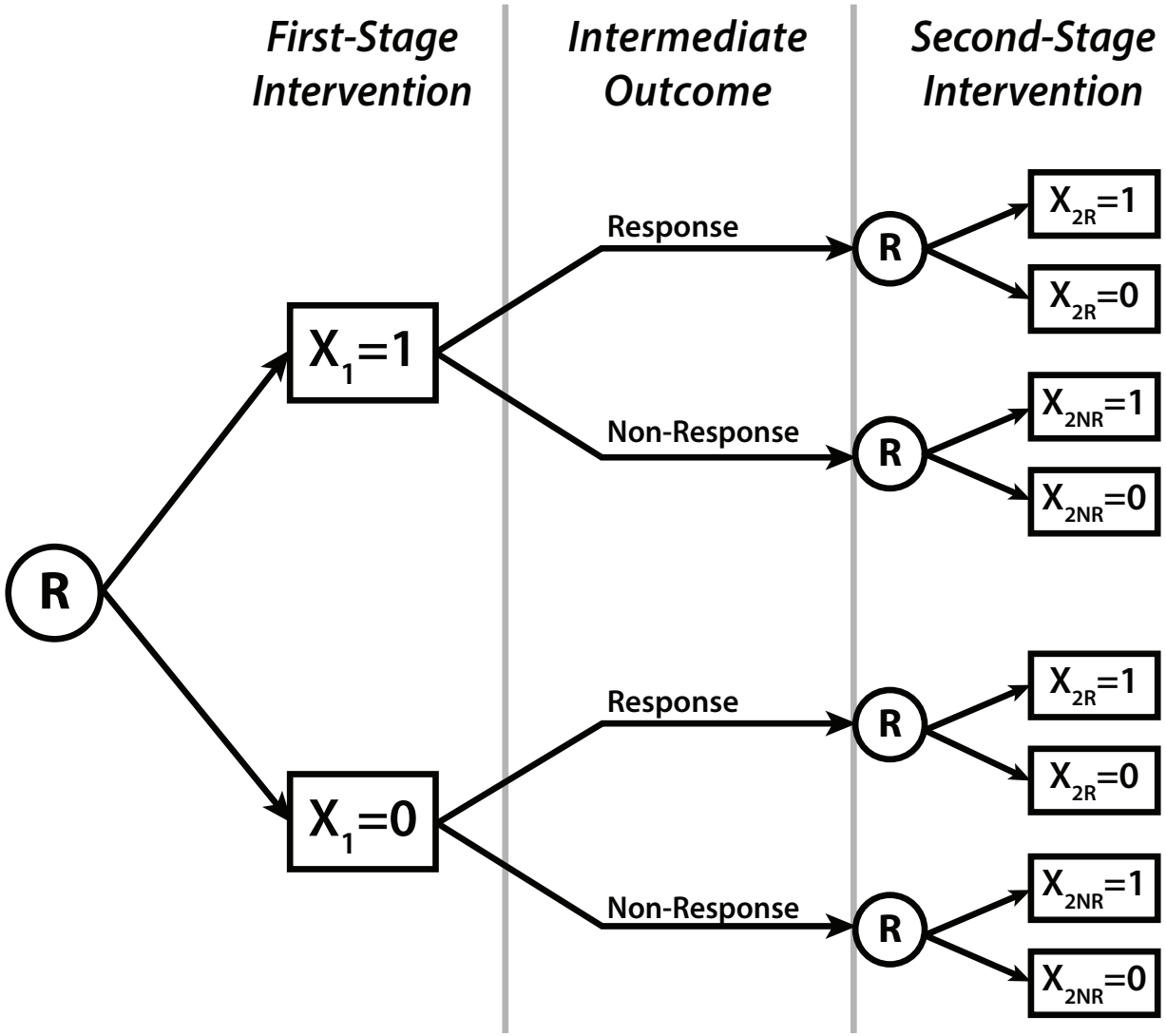
Sequential Multiple Assignment Randomized Trials

- A type of multi-stage randomized design
- Trial participants are randomized to a set of treatment options at **critical decision points** over the course of treatment
- **All individuals** participate in all stage of the trial
- Subsequent randomization is based on information leading up to that point (tailor treatment)
- DTRs are **embedded** in the design

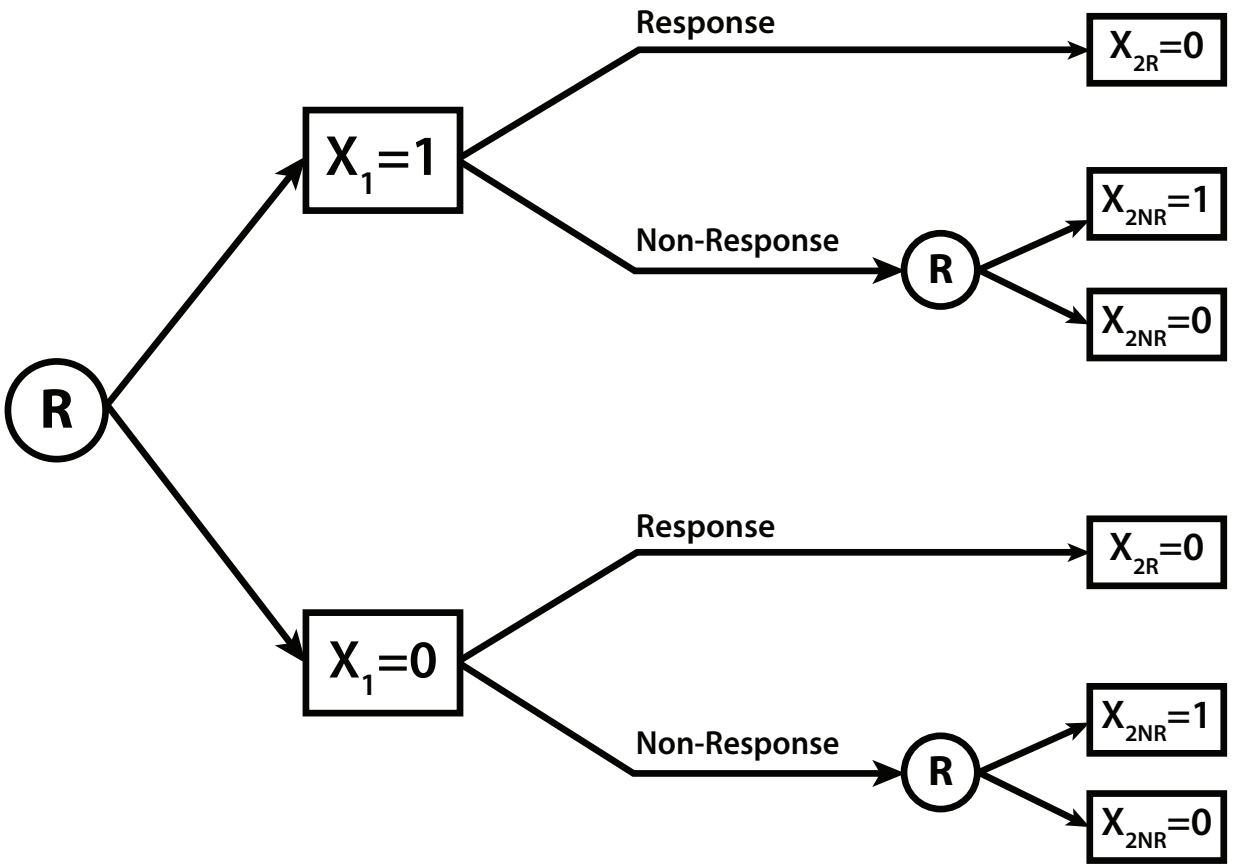
Sequential Multiple Assignment Randomized Trials

- Inform the **development of DTRs** that will mimic the treatment process
- Evaluate the **timing, sequencing and tailored selection of treatments** through randomization
- Collect information on other variables (besides tailoring variable of interest) and use observed data to estimate more **personalized decision rules**
- Develop a proposal for a DTR, which could then be tested in a 2-arm randomized trial against an appropriate alternative

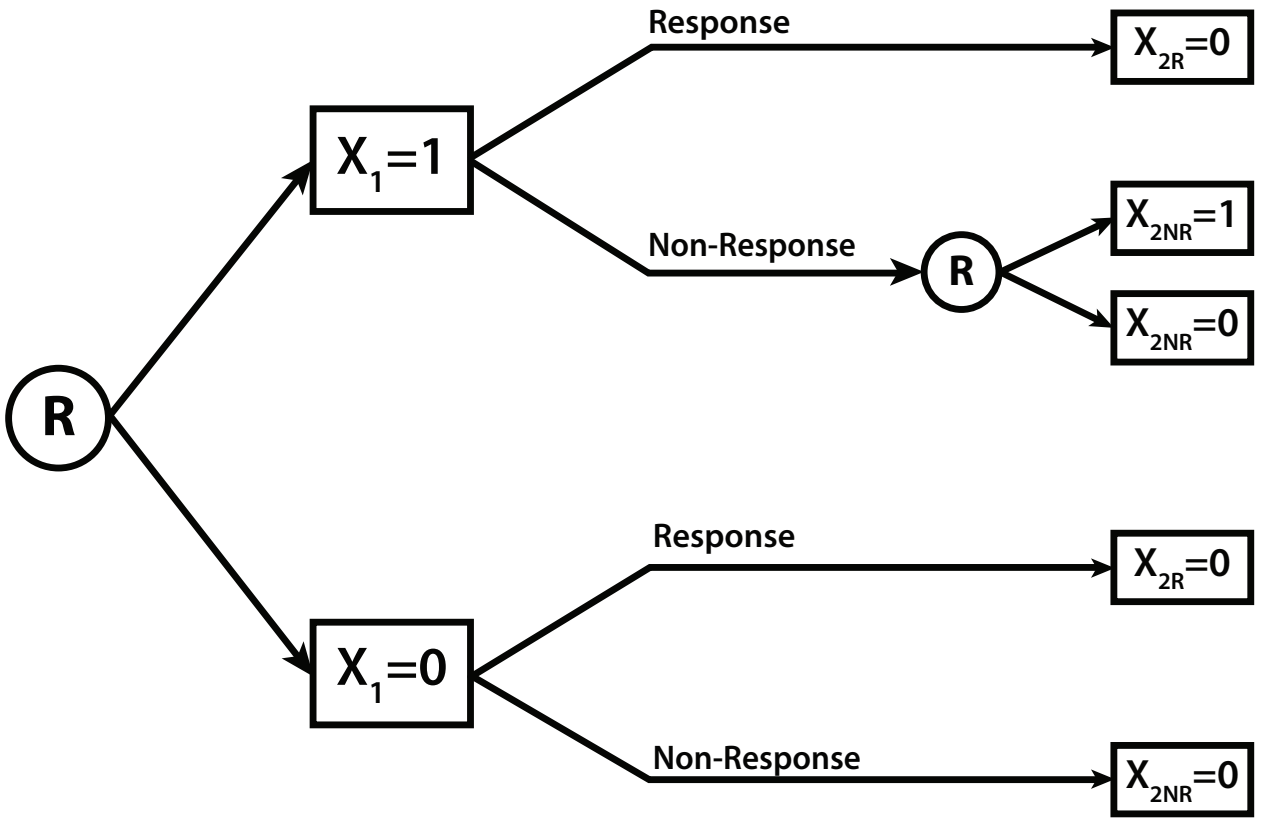
SMART EXAMPLE: 1



SMART EXAMPLE: 2



SMART EXAMPLE: 3



SMARTs in the Field

- Oncology
- Mental Health: Drug abuse, ADHD, Alcoholism, OCD, Autism, Schizophrenia, Depression, Insomnia, Bipolar, Conduct Problems, Smoking Cessation
- Prevention Research
- Obesity

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

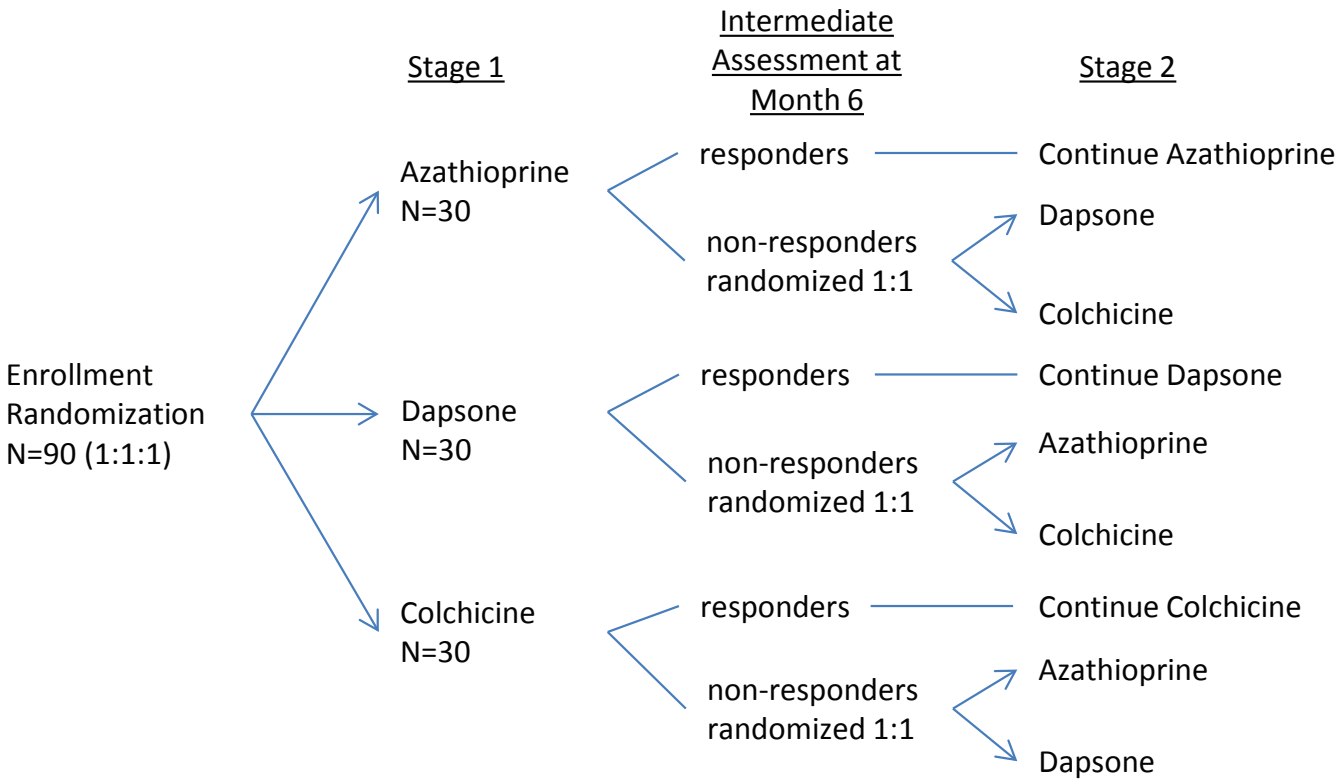
SMART Benefits

- **Delayed Effects**- treatment synergies or antagonisms
- **Prescriptive Effects**- initial treatment may elicit symptoms to better match individual to subsequent
- **Sample Selection Effects**- individuals who enroll in, remain in or are adherent in a SMART may be different from those in other designs

SMART Design Principles

- Keep it simple, straightforward
- Power for simple important primary hypothesis
- Take appropriate steps to develop a more deeply personalized DTR

SMALL N SMART



SMALL N SMART

- Goal: Compare treatments by pooling data from both stages to **find 1 optimal treatment**
- Outcome: binary- response at 6 months
- Approach: **Bayesian Joint Stage Model**- first-stage outcome is bernoulli and the second-stage outcome is modeled conditionally on the first-stage outcome using linkage parameters; **include researchers' opinions** about response rate

snSMART: Notation

- **Primary Interest**: π_k = response rate associated with the first stage treatment k
- $\beta_{0k}\pi_{k'}$ = response rate associated with second stage treatment k' after **non-response** on treatment k in stage 1
- $\beta_{1k}\pi_k$ = response rate associated with second stage treatment k after **response** on treatment k in stage 1

snSMART: Assumptions for Linkage Parameters

- $\beta_{0k} \leq 1$: Response rate in Stage 2 for treatment k is **lower** than the response rate for treatment k in stage 1
- $\beta_{1k} \geq 1$: Maintenance response rate in Stage 2 for k is **higher** in Stage 2 than the response rate in stage 1
- Model the data assuming $\beta_{0k} = \beta_0$ and $\beta_{1k} = \beta_1$

snSMART: Choice of Priors

- $\pi_k \sim Beta(0.4, 1.6)$: ARAMIS investigators felt an ineffective treatment would have spontaneous response rate of 0.20
- $\beta_0 \sim Beta(1, 1)$: equivalent to a uniform(0,1)
- $\beta_1 \sim Pareto(3, 1)$: on average the second stage response rate for responders is 1.5 times as large as the first stage response rate

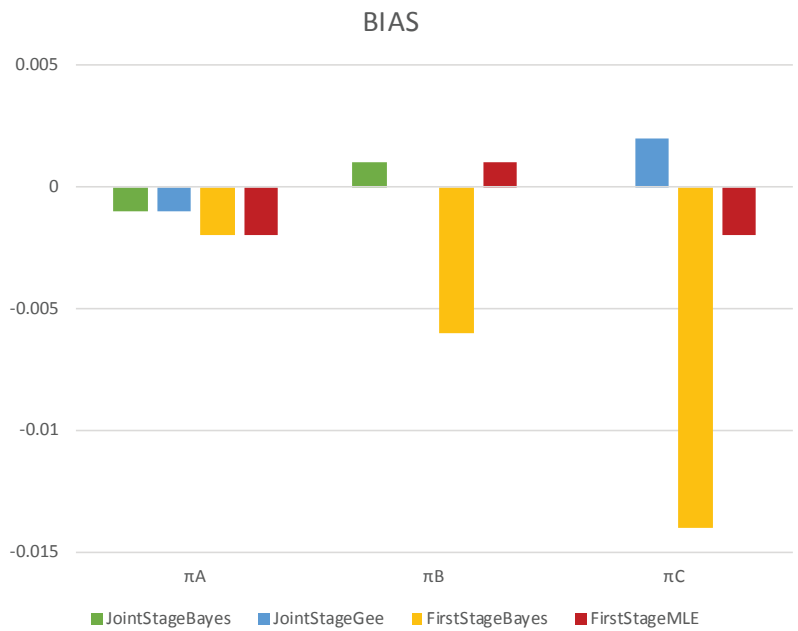
snSMART: Comparator Models

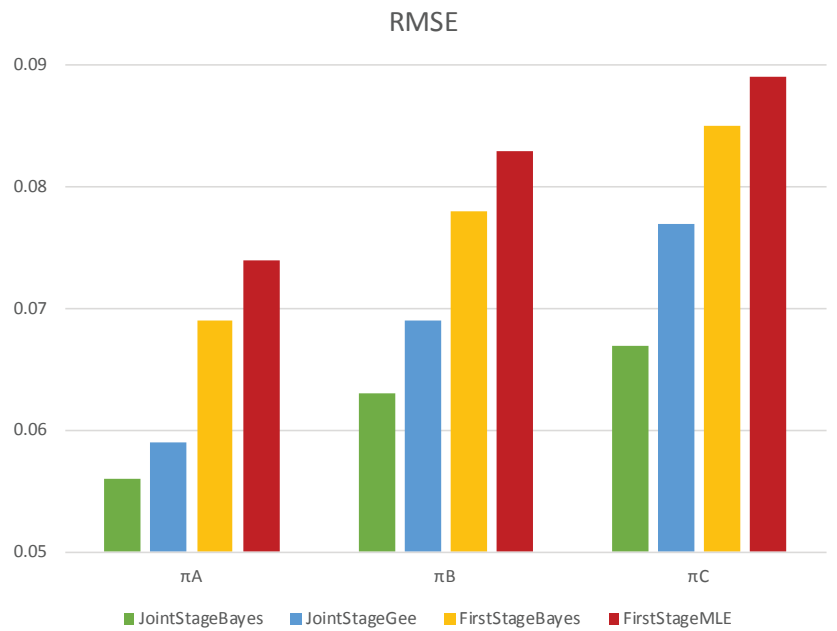
- **Joint Stage Quasi-Likelihood model**: log-Poisson GEE approach where marginal probabilities of Stage 1 and 2 are estimated + empirical estimate of correlation
- **First Stage Bayesian model**
- **First Stage MLE**

snSMART: Simulations

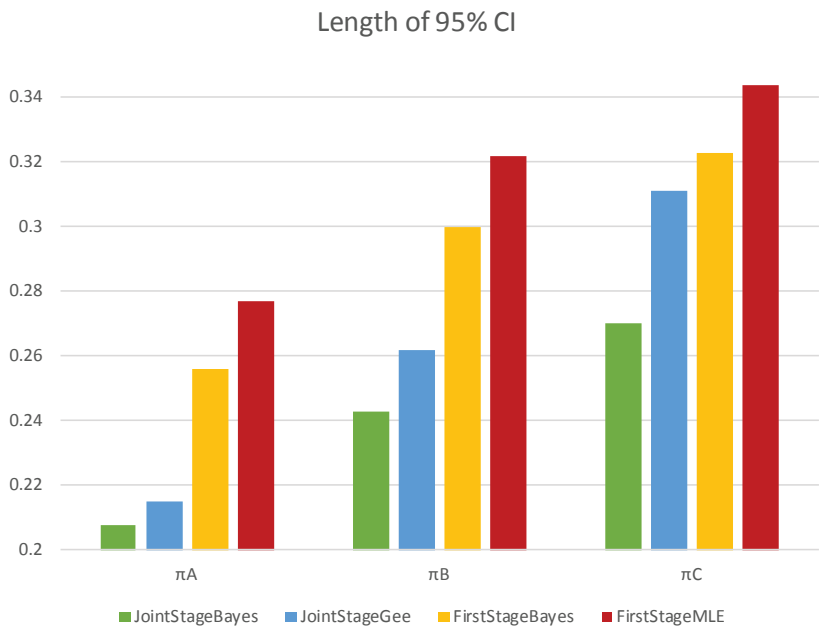
- n=90
- Response rates: $\pi_A = 0.2$, $\pi_B = 0.3$, $\pi_C = 0.4$
- **Assumptions met**: $\beta_{0A} = \beta_{0B} = \beta_{0C} = 0.6$; $\beta_{1A} = \beta_{1B} = \beta_{1C} = 1.5$
- **Assumptions Violated**: $\beta_{0A} = 0.9$; $\beta_{0B} = 0.6$ $\beta_{0C} = 0.3$; $\beta_{1A} = 1.2$, $\beta_{1B} = 1.5$, $\beta_{1C} = 1.8$

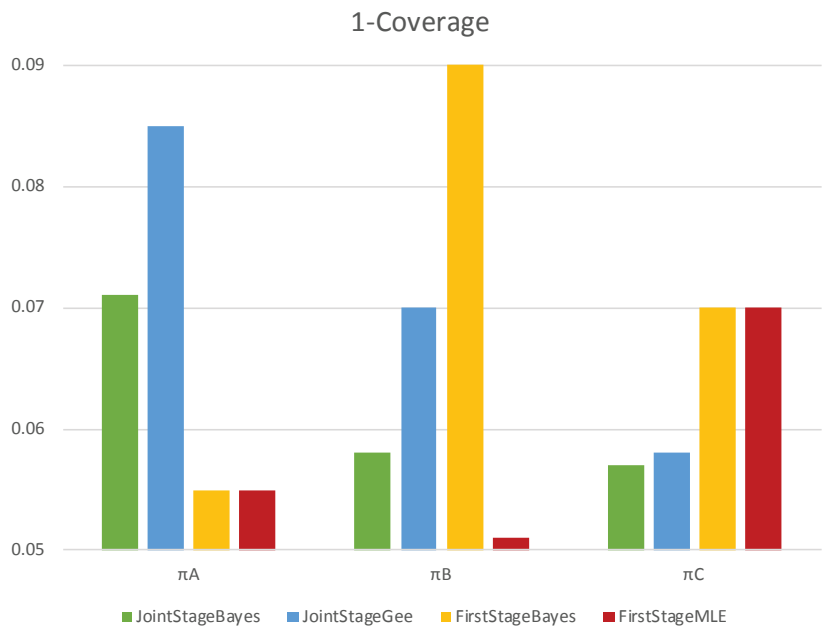
snSMART: Results: Assumptions Met



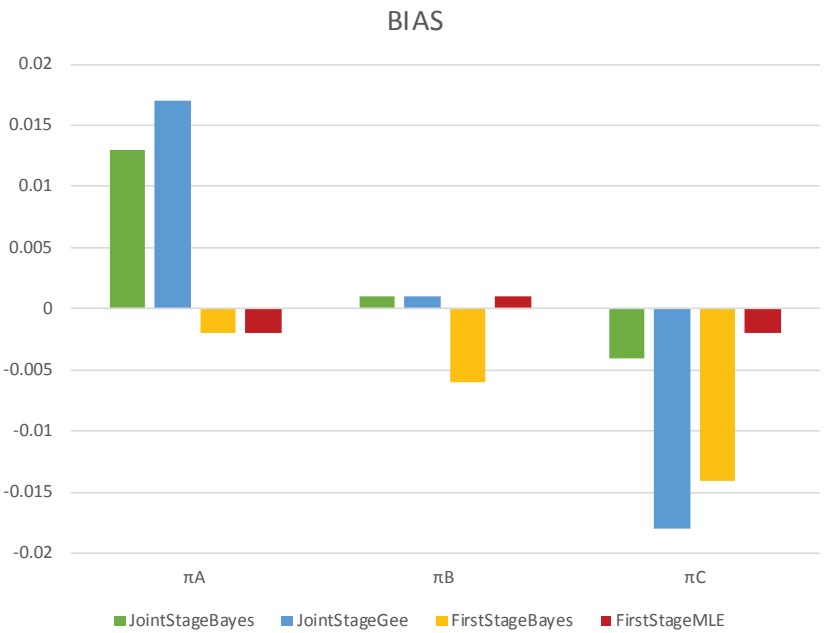


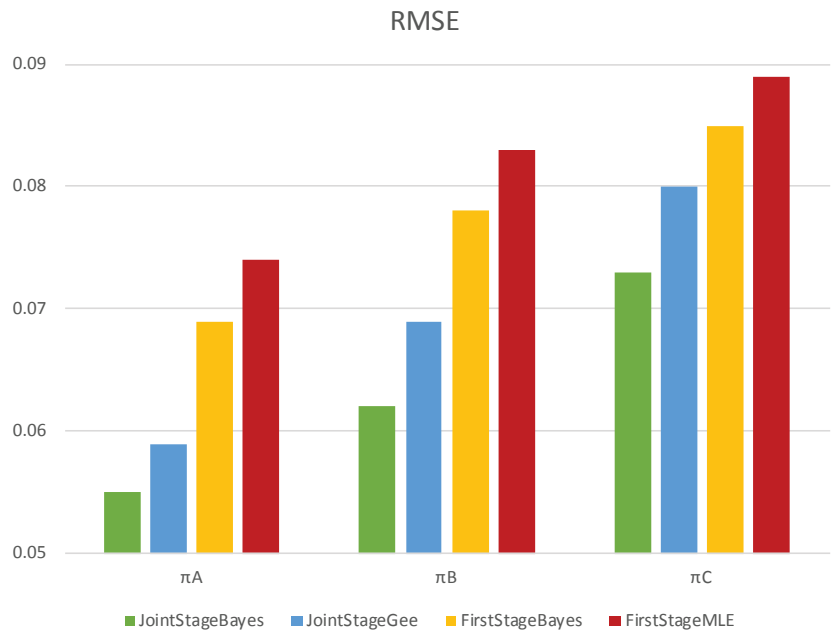
snSMART: Results: Assumptions Met



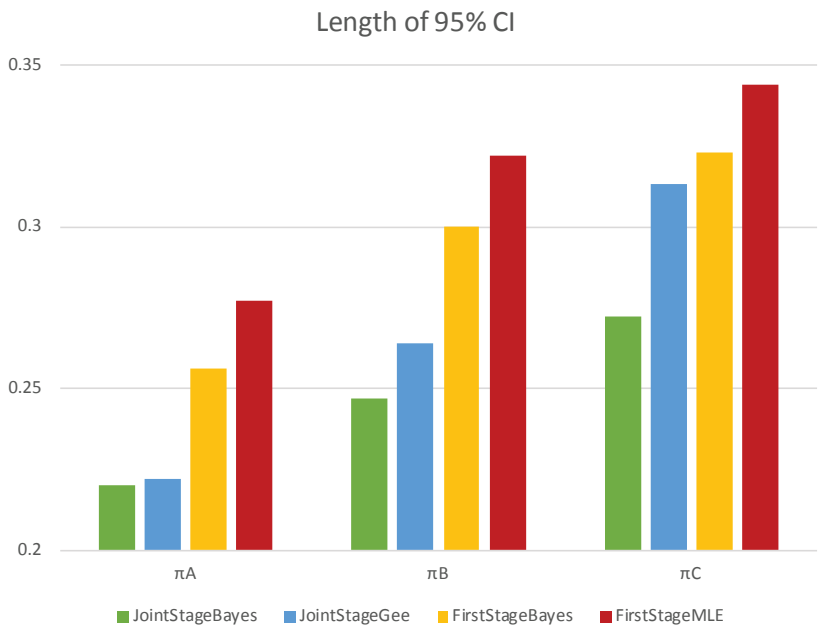


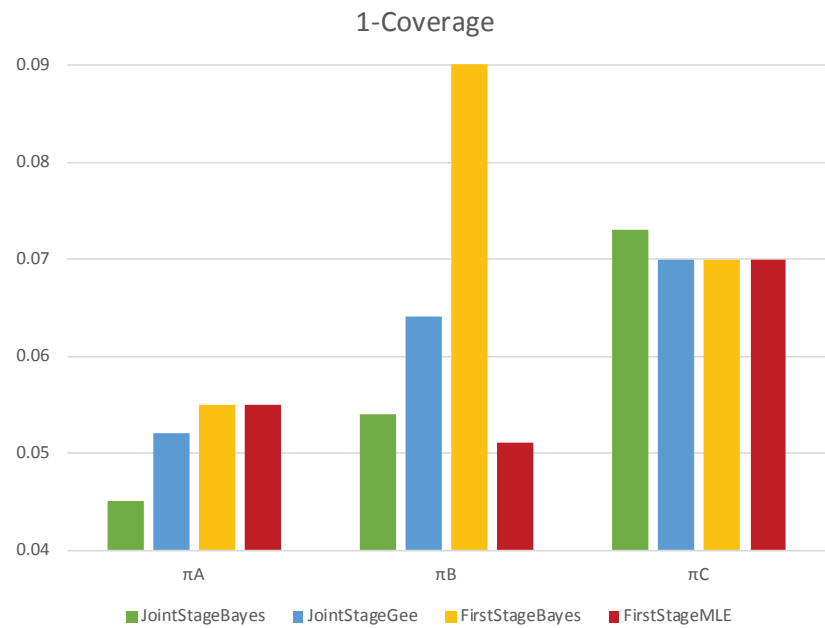
snSMART: Results: Assumptions Violated





snSMART: Results: Assumptions Violated





CONCLUSIONS: SNSMART

- Stage 2 data from a snSMART can improve inference for Stage 1 parameters
- Our proposed Joint Stage Bayes method is superior to a Quasi-Likelihood GEE approach and first stage only approaches
- For n=180, the Joint Stage Bayes approach remains superior
- Future work: differing outcomes, sample size calculator

Conclusions: SMART

- Dynamic treatment regimens are guidelines for clinical practice
- A SMART is a clinical trial design that can build better DTRs
- SMARTs do not need to be complicated or require larger sample sizes

Resources: Websites and Articles

- `https://methodology.psu.edu/ra/adap-inter/projects`
- `https://sites.google.com/a/umich.edu/kidwell/`
- Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A 'SMART' design for building individualized treatment sequences. *The Annual Review of Clinical Psychology*, 2012. 8:21-48.
- Almirall, D., Nahum-Shani, I., Sherwood, N.E., Murphy, S.A. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *Translational Behavioral Medicine*, 2014. 4(3):260-274.
- Chakraborty, B. and Murphy, S. A. Dynamic treatment regimes. Annual Review of Statistics and its Applications. 2014. 1:447-464.
- Nahum-Shani I, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. Psychological Methods. 2012. 17:457-477.
- Kidwell, K.M. SMART designs in cancer research: past, present and future. Clinical Trials. 2014. 11(4): 445-456.
- Lavori, P.W., Dawson, R. Introduction to Dynamic Treatment Strategies and sequential multiple assignment randomization. Clinical Trials. 2014. 11(4): 393-399.

Resources: Books

- **Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine**. Ed. Kosorok and Moodie. 2016. ASA-SIAM.
- **Statistical Methods for Dynamic Treatment Regimes: Reinforcement Learning, Causal Inference, and Personalized Medicine**.Chakraborty and Moodie. 2013. Springer.

Acknowledgement

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- All statements in this presentation, including its findings and conclusions are solely those of the authors and do not necessarily represent the views of the PCORI, its Board of Governors, or Methodology Committee.

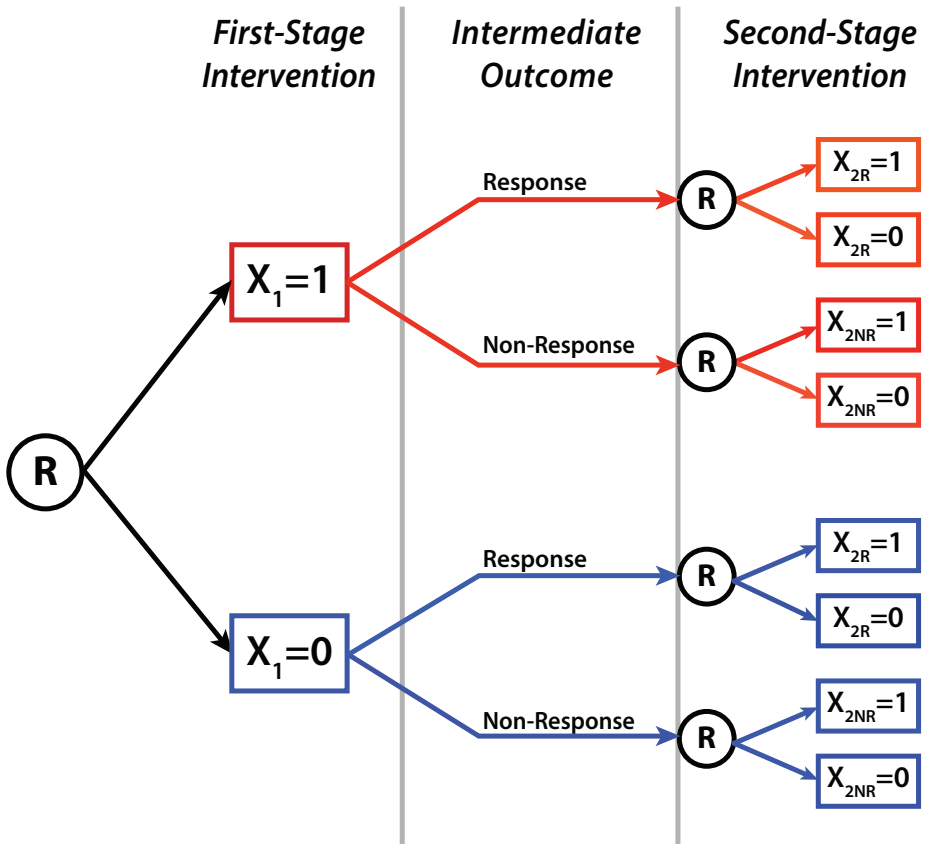
snSMART: Model

- $Y_{i1k} \sim Bernoulli(\pi_k)$, i^{th} patient at the j^{th} stage receiving treatment k
- $Y_{i2k'}|Y_{i1k} = 0 \sim Bernoulli(\beta_0 \pi_{k'})$
- $Y_{i2k}|Y_{i1k} = 1 \sim Bernoulli(\beta_1 \pi_k)$
- Priors
  - $\pi_k \sim Beta(0.4, 1.6)$, $\beta_0 \sim Beta(1, 1)$, $\beta_1 \sim Pareto(3, 1)$

SMARTs

Objectives

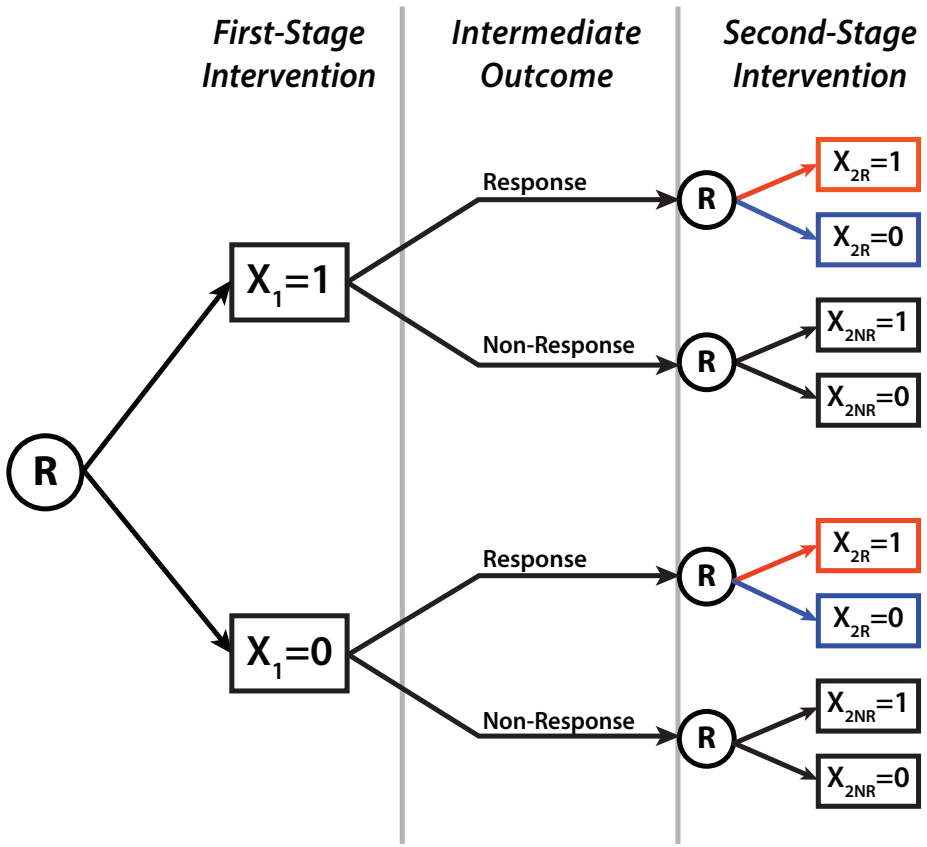
- Compare **first-stage** treatments
  - Is $X_1 = 1$ superior to $X_1 = 0$?



SMARTs

Objectives

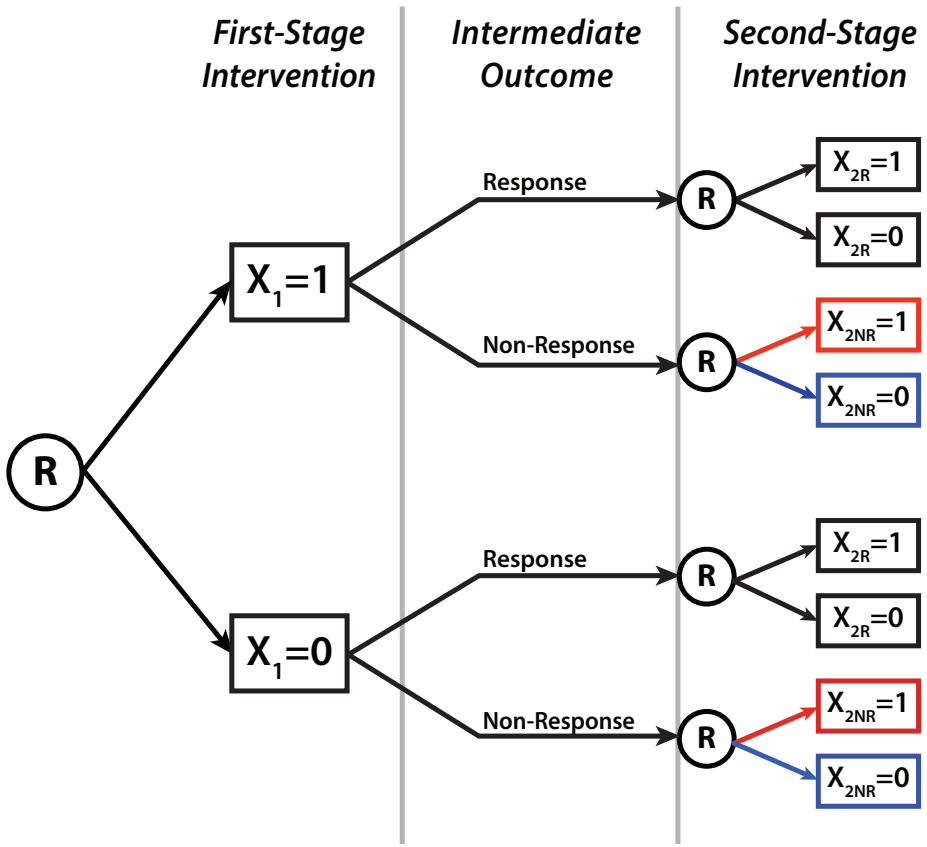
- Compare **second-stage** treatments for **responders**
  - Is $X_{2R} = 1$ superior to $X_{2R} = 0$?



SMARTs

Objectives

- Compare **second-stage** treatments for **non-responders**
  - Is $X_{2NR} = 1$ superior to $X_{2NR} = 0$?



SMARTs

Objectives

- Compare **embedded DTRs**
  - Is $(X_1 = 1, X_{2R} = 1, X_{2NR} = 1)$ superior to $(X_1 = 0, X_{2R} = 0, X_{2NR} = 0)$?
- **Optimize** DTRs
  - For whom is $(X_1 = 1, X_{2R} = 1, X_{2NR} = 1)$ most effective?