Precision Medicine: Lecture 09
SMART Design & Analysis

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Acknowledgments & Resources

Lecture drawn from:

- Kidwell, Ch. 2 of Kosorok & Moodie book: "DTRs and SMARTs: Definitions, designs, and applications"
- Petersen, et. al. Ch. 10 of Kosorok & Moodie book: "Evaluation of longitudinal dynamic regimes with and without marginal structural working models"
- Nahum-Shani, et. al. (2012), Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. *Psychol Methods*.
- Advanced Topics in Causal Inference - class by Petersen & Montoya
- "Causal Inference for Multiple Time-Point (Longitudinal) Exposures" - workshop by Balzer & Montoya

Recap Last Lecture

What is a SMART?

- Multistage trial in which treatment assignment is a function of pre-specified variable(s) measured during the trial

What data are generated from a SMART?

- Longitudinal data, where treatment is a function of pre-specified tailoring variables

What questions can we (easily) answer with a SMART?

- Causal questions ranging from point treatment, static regimes to longitudinal, dynamic regimes
- These lectures: focus on value of SMART's embedded regimes

What is required to answer these questions?

- For evaluating embedded regimes: sequential randomization assumption and sequential positivity, which hold by design with a SMART

How to answer these questions?

- This is where we left off

Outline

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Goal: Estimation of Value of One Embedded Regime

Goal is to estimate the value of each embedded regime, i.e., this statistical parameter (longitudinal g-computation formula):

$$\Psi(P_0) = \sum_{x_1,\ldots,x_K} \mathbb{E}_0 \left[Y | \bar{x}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)) \right]$$
$$\times \prod_{t=1}^{K} P_0 \left(x(t) | \bar{x}(t-1), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1)) \right)$$

Goal: Estimation of Value of One Embedded Regime

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$$\times \prod_{t=1}^{K} P_0 \left(x(t) | \bar{x}(t-1), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1)) \right)$$

or for 2 timepoints...

$$\Psi(P_0) = \sum_{x_1,x_2} \mathbb{E}_0 \left[Y | \bar{x}(2), \bar{A}(2) = \bar{d}_2(\bar{Z}(2)) \right]$$
$$\times P_0 \left(x(2) | x(1), A(1) = d_1(Z(1)) \right)$$
$$\times P_0 \left(x(1) \right)$$

Goal: Estimation of Value of One Embedded Regime

- Denote P_n as the empirical distribution based on sampling from P_0 that gives each observation weight $\frac{1}{n}$
  - Estimates from empirical distribution P_n are denoted with a subscript n
  - (contrast with true values from true data distribution P_0 are denoted with a subscript 0)
- An estimator $\hat{\Psi}$ is a mapping $\hat{\Psi} : \mathcal{M} \to \mathbb{R}$
- We will talk about 3 estimators for $\Psi(P_0)$, our statistical estimand
  - IPW estimator
  - G-computation estimator based on Iterated Conditional Expectations (ICEs)
  - Targeted Maximum Likelihood Estimator (TMLE)

IPW Estimand

The g-computation formula can be re-written as the following IPW estimand (Hernan and Robins, 2006; Rosenbaum and Rubin, 1983):

$$\mathbb{E}_0 \left[\frac{\mathbb{I}[\bar{A}(K) = \bar{d}_K(\bar{Z}(K))]Y}{\prod_{t=1}^{K} g_0(A(t) = d_t(\bar{Z}(t)) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1)))} \right]$$

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where $\prod_{t=1}^{K} g_0(A(t)=d_t(\bar{Z}(t))|\bar{X}(t),\bar{A}(t-1)=\bar{d}_{t-1}(\bar{Z}(t-1)))$ is the product of time-point-specific predicted probabilities of observed treatment, given the observed treatment and covariate history

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where $\prod_{t=1}^{K} g_0(A(t)=d_t(\bar{Z}(t))|\bar{X}(t),\bar{A}(t-1)=\bar{d}_{t-1}(\bar{Z}(t-1)))$ is the product of time-point-specific predicted probabilities of observed treatment, given the observed treatment and covariate history

or for 2 timepoints...

$$\mathbb{E}_0\left[\frac{\overbrace{\mathbb{I}[A(2)=d_2(\bar{Z}(2)),A(1)=d_1(Z(1))]}^{\text{follow the regime?}}\ \overbrace{Y}^{\text{outcome}}}{\underbrace{g_0(A(2)=d_2(\bar{Z}(2))|\bar{X}(2),A(1)=d_1(Z(1)))}_{\text{time 2}}\underbrace{g_0(A(1)=d_1(Z(1))|X(1))}_{\text{time 1}}}\right]$$

IPW Estimator

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i(K) = \bar{d}_K(\bar{Z}_i(K))]\, Y_i}{\prod_{t=1}^{K} g_n(A_i(t) = d_t(\bar{Z}_i(t)) | \bar{X}_i(t), \bar{A}_i(t-1) = \bar{d}_{t-1}(\bar{Z}_i(t-1)))}$$

IPW Estimation

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i(K) = \bar{d}_K(\bar{Z}_i(K))]Y_i}{\prod_{t=1}^{K} g_n(A_i(t) = d_t(\bar{Z}_i(t))|\bar{X}_i(t), \bar{A}_i(t-1) = \bar{d}_{t-1}(\bar{Z}_i(t-1)))}$$

Intuition:

- Confounding as a problem of biased sampling
  - Certain exposure-covariate subgroups are over-represented
  - Other exposure-covariate subgroups are under-represented
- Apply weights to up-weight under-represented observations and down-weight over-represented observations
- Average weighted outcomes (giving weight 0 to those who do not follow regime)

IPW Estimation

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i(K) = \bar{d}_K(\bar{Z}_i(K))]Y_i}{\prod_{t=1}^{K} g_n(A_i(t) = d_t(\bar{Z}_i(t))|\bar{X}_i(t), \bar{A}_i(t-1) = \bar{d}_{t-1}(\bar{Z}_i(t-1)))}$$

In a SMART, the treatment mechanism is known; thus, if there is no censoring, one could use:

- the true g_0
- g_n could be a maximum likelihood estimator (MLE) based on a correctly specified parametric model

IPW Estimation

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i(K) = \bar{d}_K(\bar{Z}_i(K))]Y_i}{\prod_{t=1}^{K} g_n(A_i(t) = d_t(\bar{Z}_i(t))|\bar{X}_i(t), \bar{A}_i(t-1) = \bar{d}_{t-1}(\bar{Z}_i(t-1)))}$$

Do you see any potential dangers with this IPW estimator in a longitudinal observational study?

IPW Estimation

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i(K) = \bar{d}_K(\bar{Z}_i(K))]Y_i}{\prod_{t=1}^{K} g_n(A_i(t) = d_t(\bar{Z}_i(t))|\bar{X}_i(t), \bar{A}_i(t-1) = \bar{d}_{t-1}(\bar{Z}_i(t-1)))}$$

In a longitudinal study with several time points, in the denominator one is multiplying several probabilities together $\implies$ very small denominator $\implies$ large weights $\implies$ instability of estimator/large variance

IPW: One way forward...

Stabilized (modified Horvitz-Thompson) estimator:

$$\hat{\Psi}_d(P_n) = \frac{\frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i = \bar{d}_K(\bar{Z}_i(K))]Y_i}{\prod_{t=1}^{K} g_n(A_i(t)=d_t(\bar{Z}_i(t))|\bar{X}_i(t),\bar{A}_i(t-1)=\bar{d}_{t-1}(\bar{Z}_i(t-1)))}}{\frac{1}{n}\sum_{i=1}^{n} \frac{\mathbb{I}[\bar{A}_i = \bar{d}_K(\bar{Z}_i(K))]}{\prod_{t=1}^{K} g_n(A_i(t)=d_t(\bar{Z}_i(t))|\bar{X}_i(t),\bar{A}_i(t-1)=\bar{d}_{t-1}(\bar{Z}_i(t-1)))}}$$

This is the IPW estimator, but divided by the sample average of the weights. Advantages:

- Reduction in the variability of the IPW estimates
- Containment in the parameter space (e.g., if Y is binary, it will ensure an estimate between 0 and 1)

G-comp. estimand based on ICEs

$$\sum_{x_1,\ldots,x_K} \mathbb{E}_0\left[Y|\bar{x}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))\right]$$
$$\times \prod_{t=1}^{K} P_0\left(x(t)|\bar{x}(t-1), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))\right)$$

(g-computation formula) can be re-written as the following iterated conditional expectations (ICEs) (Bang and Robins, 2005):

$$\mathbb{E}_0[\mathbb{E}_0[\ldots$$
$$\mathbb{E}_0\left[\mathbb{E}_0\left[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))\right]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))\right]$$
$$\ldots|X(1), A(1) = d_1(Z(1))]]$$

G-comp. estimand based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K),\bar{A}(K)=\bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1),\bar{A}(K-1)=\bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1),A(1)=d_1(Z(1))]]$$

G-comp. estimand based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[\underbrace{Y}_{\text{outcome}} \mid \underbrace{\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))}_{\text{history before } t = K+1 \text{ at regime}}]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1), A(1) = d_1(Z(1))]]$$

G-comp. estimand based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\ldots \mathbb{E}_0[\underbrace{\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]}_{\text{pseudo-outcome}} \underbrace{|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]}_{\text{history before } t = K \text{ at regime}} \ldots |X(1), A(1) = d_1(Z(1))]]$$

G-comp. estimand based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\underbrace{\cdots}_{t=3,\ldots,K\text{-}1} \mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))] \underbrace{\cdots}_{t=3,\ldots,K\text{-}1} |X(1), A(1) = d_1(Z(1))]]$$

G-comp. estimand based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\underbrace{\ldots \mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))] \ldots}_{\text{pseudo-outcome}}| \underbrace{X(1), A(1) = d_1(Z(1))}_{\text{history before } t=2 \text{ at regime}}]]$$

G-comp. estimand based on ICEs

$$\underbrace{\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K),\bar{A}(K)=\bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1),\bar{A}(K-1)=\bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1),A(1)=d_1(Z(1))]]}_{\text{standardize over baseline covariate distribution } X(1)}$$

G-comp. estimand based on ICEs

To estimate these iterated conditional expectations, one can fit a series of regressions going backwards in time, where each regression uses the regression before it (evaluated at the covariate history and treatment rule of interest) as a pseudo-outcome

$$\mathbb{E}_0[\mathbb{E}_0[\ldots \mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))] \ldots |X(1), A(1) = d_1(Z(1))]]$$

ICE G-comp Est. Implementation

$$\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[\underbrace{Y}_{\text{outcome}} \mid \underbrace{\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))}_{\text{history before } t = K+1 \text{ at regime}}]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1), A(1) = d_1(Z(1))]]$$

1. At $t = K + 1$: Estimate the innermost conditional mean outcome, i.e.,

$$\begin{aligned}&\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]\\ \equiv &Q_{0,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))\end{aligned}$$

1.1 Regress the outcome Y on all past history, i.e., $\bar{X}(K)$ and $\bar{A}(K)$

1.2 Predict at the regime of interest $\bar{A}(K) = \bar{d}_K(\bar{Z}(K))$ to obtain

$$\begin{aligned}&\mathbb{E}_n[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]\\ \equiv &Q_{n,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))\end{aligned}$$

ICE G-comp Est. Implementation

$$\mathbb{E}_0[\mathbb{E}_0[\ldots \mathbb{E}_0[\underbrace{\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]}_{\text{pseudo-outcome}} \underbrace{|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]}_{\text{history before } t=K \text{ at regime}} \ldots |X(1), A(1) = d_1(Z(1))]]$$

2. At $t = K$: Estimate the next conditional expectation

$$\mathbb{E}_0\left[Q_{0,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))\right]$$
$$\equiv Q_{0,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$$

2.1 Regress the pseudo-outcome from the previous step $Q_{n,K+1}$ on past history before time K, i.e., $\bar{X}(K-1)$ and $\bar{A}(K-1)$.

2.2 Predict at the embedded regime of interest $\bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))$ to obtain

$$\mathbb{E}_n\left[Q_{n,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))\right]$$
$$\equiv Q_{n,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$$

ICE G-comp Est. Implementation

$$\mathbb{E}_0[\mathbb{E}_0[\underbrace{\ldots \mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))] \ldots}_{\text{pseudo-outcome}}| \underbrace{X(1), A(1) = d_1(Z(1))}_{\text{history before } t=2 \text{ at regime}}]]$$

3. ...
4. At $t = 2$: Estimate

$$\mathbb{E}_0\left[\ldots Q_{0,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))) \ldots |X(1), A(1) = d_1(Z(1))\right]$$
$$\equiv Q_{0,2}(X(1), A(1) = d_1(Z(1)))$$

4.1 Regress the pseudo-outcome from the previous step $Q_{n,3}$ on past history before time 2, i.e., $X(1)$ and $A(1)$.

4.2 Predict at the embedded regime of interest $A(1) = d_1(Z(1))$ to obtain

$$\mathbb{E}_n\left[\ldots Q_{n,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))) \ldots |X(1), A(1) = d_1(Z(1))\right]$$
$$\equiv Q_{n,2}(X(1), A(1) = d_1(Z(1)))$$

ICE G-comp Est. Implementation

$$\underbrace{\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K),\bar{A}(K)=\bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1),\bar{A}(K-1)=\bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1),A(1)=d_1(Z(1))]]}_{\text{standardize over baseline covariate distribution } X(1)}$$

5. At $t = 1$: Estimate $\Psi_d(P_0)$.
   5.1 Standardize the pseudo-outcomes from the previous step with respect to the distribution of baseline covariates $X(1)$ by taking the empirical average of $Q_{n,2}(X(1), A(1) = d_1(Z(1)))$ to obtain $\hat{\Psi}_d(P_n)$.

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} Q_{n,2}(X_i(1), A_i(1) = d_1(Z_i(1)))$$

TMLE based on ICEs

- Combines the treatment mechanisms estimated in the IPW estimator with the ICEs estimated in the g-computation estimator
- Same as ICE g-computation estimation procedure, except that each regression at time t is updated before using it as an outcome for the next regression corresponding to time $t-1$

TMLE based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[\underbrace{Y}_{\text{outcome}} \mid \underbrace{\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))}_{\text{history before } t = K+1 \text{ at regime}}]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1), A(1) = d_1(Z(1))]]$$

1. At $t = K + 1$
   a. Generate an initial estimate of $Q_{0,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))$ to obtain:

$$\begin{aligned}&\mathbb{E}_n^0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]\\ \equiv &Q_{n,K+1}^0(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))\end{aligned}$$

   b. Update $Q_{n,K+1}^0$ to $Q_{n,K+1}^\star$ as follows:
      i. Fit a logistic regression of Y on the intercept using $Q_{n,K+1}^0(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))$ as offset and weight $\mathbb{I}[\bar{A}(K) = \bar{d}_K(\bar{Z}(K))]/\prod_{t=1}^K g_n(A(t) = d_t(\bar{Z}(t))|\bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(Z(t-1)))$
      ii. Predict the logistic regression fit in step 1b at $\bar{A}(K) = \bar{d}_K(\bar{Z}(K))$ to obtain the targeted estimate $Q_{n,K+1}^*(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))$

TMLE based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\ldots \mathbb{E}_0[\underbrace{\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]}_{\text{pseudo-outcome}} \underbrace{|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]}_{\text{history before } t = K \text{ at regime}} \ldots |X(1), A(1) = d_1(Z(1))]]$$

2. At $t = K$
   a. Using $Q^{\star}_{n,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))$ from the previous step as a pseudo-outcome, generate an initial estimate of $Q_{0,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$:

$$\mathbb{E}^0_n[Q^{\star}_{n,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]$$
$$\equiv Q^0_{n,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$$

   b. Update $Q^0_{n,K}$ to $Q^{\star}_{n,K}$ as follows:
      i. Fit a logistic regression of $Q^*_{n,K+1}(\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K)))$ on the intercept using $Q^0_{n,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$ as offset and weight $\mathbb{I}[\bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))]/\prod_{t=1}^{K-1} g_n(A(t) = d_t(\bar{Z}(t))|\bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(Z(t-1)))$
      ii. Predict the logistic regression fit in step 2b at $\bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$ to obtain the targeted estimate $Q^*_{n,K}(\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1)))$

TMLE based on ICEs

$$\mathbb{E}_0[\mathbb{E}_0[\underbrace{\ldots \mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K), \bar{A}(K) = \bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1), \bar{A}(K-1) = \bar{d}_{K-1}(\bar{Z}(K-1))] \ldots}_{\text{pseudo-outcome}}| \underbrace{X(1), A(1) = d_1(Z(1))}_{\text{history before } t=2 \text{ at regime}}]]$$

3. ...
4. At $t = 2$
   a. Using $Q^{\star}_{n,3}(\bar{X}(2), \bar{A}(2) = \bar{d}_2(\bar{Z}(2)))$ from the previous step as a pseudo-outcome, generate an initial estimate of $Q_{0,2}(X(1), A(1) = d_1(Z(1)))$:

$$\begin{aligned} &\mathbb{E}^0_n[Q^{\star}_{n,3}(\bar{X}(2), \bar{A}(2) = \bar{d}_2(\bar{Z}(2)))|X(1), A(1) = d_1(Z(1))] \\ \equiv &Q^0_{n,2}(X(1), A(1) = d_1(Z(1))) \end{aligned}$$

   b. Update $Q^0_{n,2}$ to $Q^{\star}_{n,2}$ as follows:
      i. Fit a logistic regression of $Q^{*}_{n,3}(\bar{X}(2), \bar{A}(2) = \bar{d}_2(\bar{Z}(2)))$ on the intercept using $Q^0_{n,2}(X(1), A(1) = d_1(Z(1)))$ as offset and weight $\mathbb{I}[A(1) = d_1(Z(1))]/g_n(A(1) = d_1(Z(1))|X(1))$
      ii. Predict the logistic regression fit in step 4b at $A(1) = d_1(Z(1)))$ to obtain the targeted estimate $Q^{*}_{n,2}(X(1), A(1) = d_1(Z(1)))$

TMLE based on ICEs

$$\underbrace{\mathbb{E}_0[\mathbb{E}_0[\ldots\mathbb{E}_0[\mathbb{E}_0[Y|\bar{X}(K),\bar{A}(K)=\bar{d}_K(\bar{Z}(K))]|\bar{X}(K-1),\bar{A}(K-1)=\bar{d}_{K-1}(\bar{Z}(K-1))]\ldots|X(1),A(1)=d_1(Z(1))]]}_{\text{standardize over baseline covariate distribution } X(1)}$$

5. At $t = 1$: Estimate $\Psi_d(P_0)$
   a. Standardize the pseudo-outcomes from the previous step with respect to the distribution of baseline covariates $X(1)$ by taking the empirical average of $Q^*_{n,2}(X(1), A(1) = d_1(Z(1)))$ to obtain $\hat{\Psi}_d(P_n)$

$$\hat{\Psi}_d(P_n) = \frac{1}{n}\sum_{i=1}^{n} Q^*_{n,2}(X_i(1), A_i(1) = d_1(Z_i(1)))$$

Outline

Brief Review - Asymptotic Linearity

An estimator $\hat{\Psi}$ is asymptotically linear (AL) with for its true value $\Psi(P_0)$ if it can be written in the following form:

$$\hat{\Psi}(P_n) - \Psi(P_0) = \frac{1}{n}\sum_{i=1}^{n} IC(O_i) + o_P(1/\sqrt{n})$$

- Where
  - $IC(O_i)$ is the estimator's influence curve/function
- An AL estimator thus generally has the following properties (under regularity conditions):
  - its bias converges to 0 in sample size at a rate faster than $\frac{1}{\sqrt{n}}$
  - σ_0^2 can be well-approximated by the sample variance of the estimated influence curve
  - for large n, its distribution is approximately normal, $n^{1/2}(\hat{\Psi}(P_n) - \Psi(P_0)) \xrightarrow{d} N(0, \sigma_0^2)$, allowing an estimate of σ_0^2 to be used to construct a Wald-type confidence intervals

Conditions for AL w.r.t. $\Psi_d(P_0)$

- ICE G-comp?
- IPW?
- TMLE?

Conditions for AL w.r.t. $\Psi_d(P_0)$

- ICE G-comp - AL if Q factors known or estimated with maximum likelihood estimate (MLE) of Q_0 based on correctly specified parametric models
  - We cannot guarantee this with our knowledge of how SMART data were generated
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  - However, not asymptotically efficient

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- IPW - AL if g factors known or estimated with MLE of g_0 based on correctly specified parametric models
  - We know these with SMART data
  - However, not asymptotically efficient
- TMLE - double robust. AL if either Q factors or g factors are known/estimated consistently
  - If both known and/or estimated consistently and at reasonable rates, it is efficient
  - Can use ML to estimate Q (or if unknown, g) factors
  - Also, a substitution estimator (respects parameter space, improved stability)

IC for Value of One Embedded Regime

In a SMART with no censoring (i.e., g factors are known), the efficient influence curve of
$IC^*_d(P)(O) = \sum_{t=1}^{K} IC^*_{d_t}(Q,g)(O) + Q_2(X(1), d_1(Z(1))) - \Psi_d(P)$,
where:

$$IC^*_{d_K}(O) = \frac{\mathbb{I}[\bar{A}(K) = \bar{d}_K(\bar{Z}(K))](Y - Q_{K+1}(\bar{X}(K), \bar{d}_K(\bar{Z}(K)))}{\prod_{t=1}^{K} g(A(t)|\bar{X}(t), \bar{A}(t-1))},$$

and, for $t = 1, ..., K-1$:

$$IC^*_{d_t}(O) = \frac{\mathbb{I}[\bar{A}(t) = \bar{d}_t(\bar{Z}(t))](Q_{t+2}(\bar{X}(t+1), \bar{d}_{t+1}(\bar{Z}(t+1))) - Q_{t+1}(\bar{X}(t), \bar{d}_t(\bar{Z}(t))))}{\prod_{j=1}^{t} g(A(j)|\bar{X}(j), \bar{A}(j-1))}$$

Inference for Value of One Embedded Regime

We obtain inference on the value of **one** embedded regime d by a constructing confidence interval in the following way:

$$\hat{\Psi}_d(P_n) \pm \Phi^{-1}(0.975)\frac{\hat{\sigma}_d}{\sqrt{n}},$$

where $\hat{\sigma}_d^2 = \frac{1}{n}\sum_{i=1}^{n} \widehat{IC}^2(O_i)$ (mean of IC is 0, by definition)

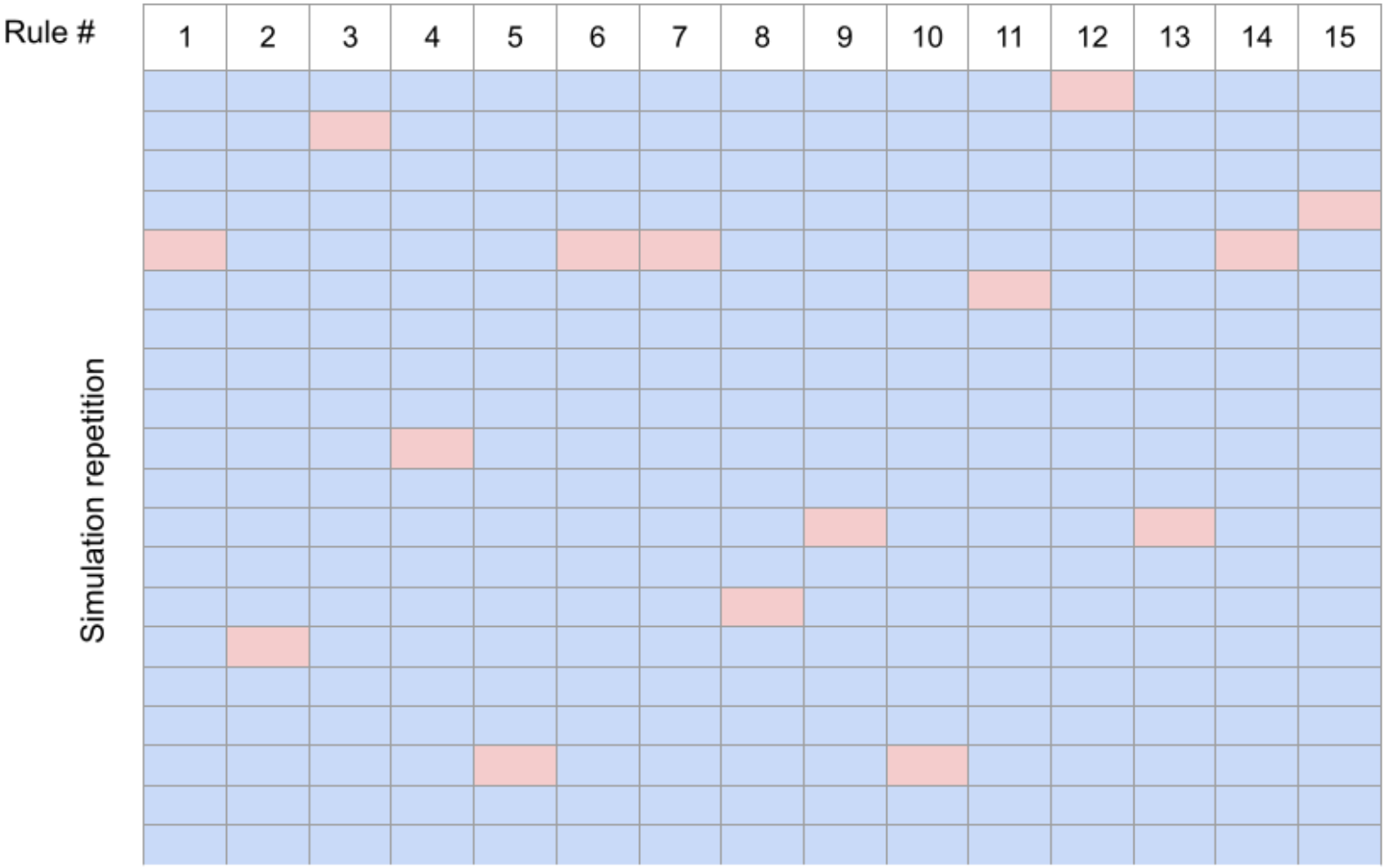
Recall...

We are interested in all values of each embedded regime, simultaneously $\Psi(P_0) = (\Psi_{d^{(1)}}(P_0), ..., \Psi_{d^{(D)}}(P_0))$

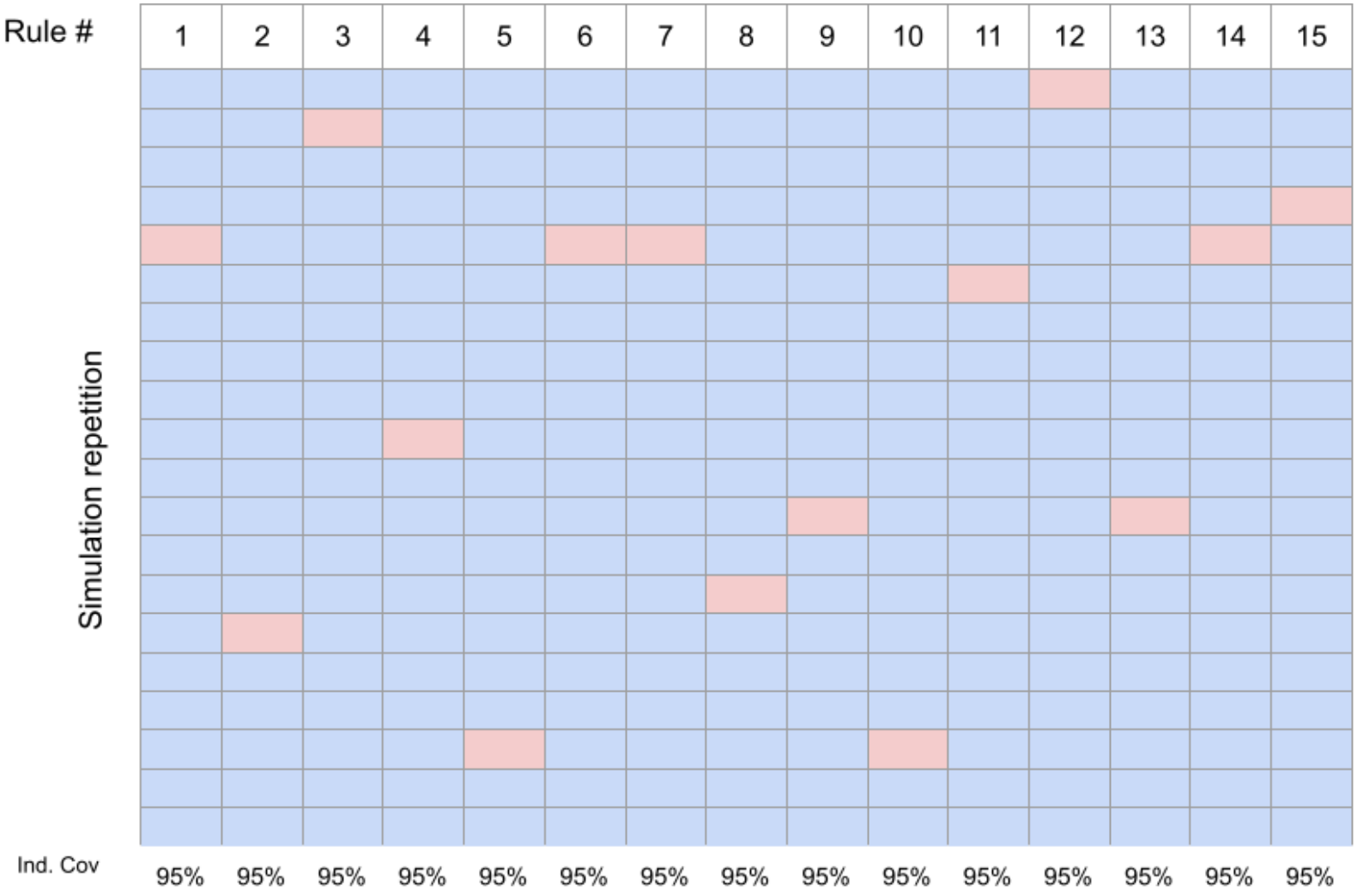
Individual Inference...

Rule #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

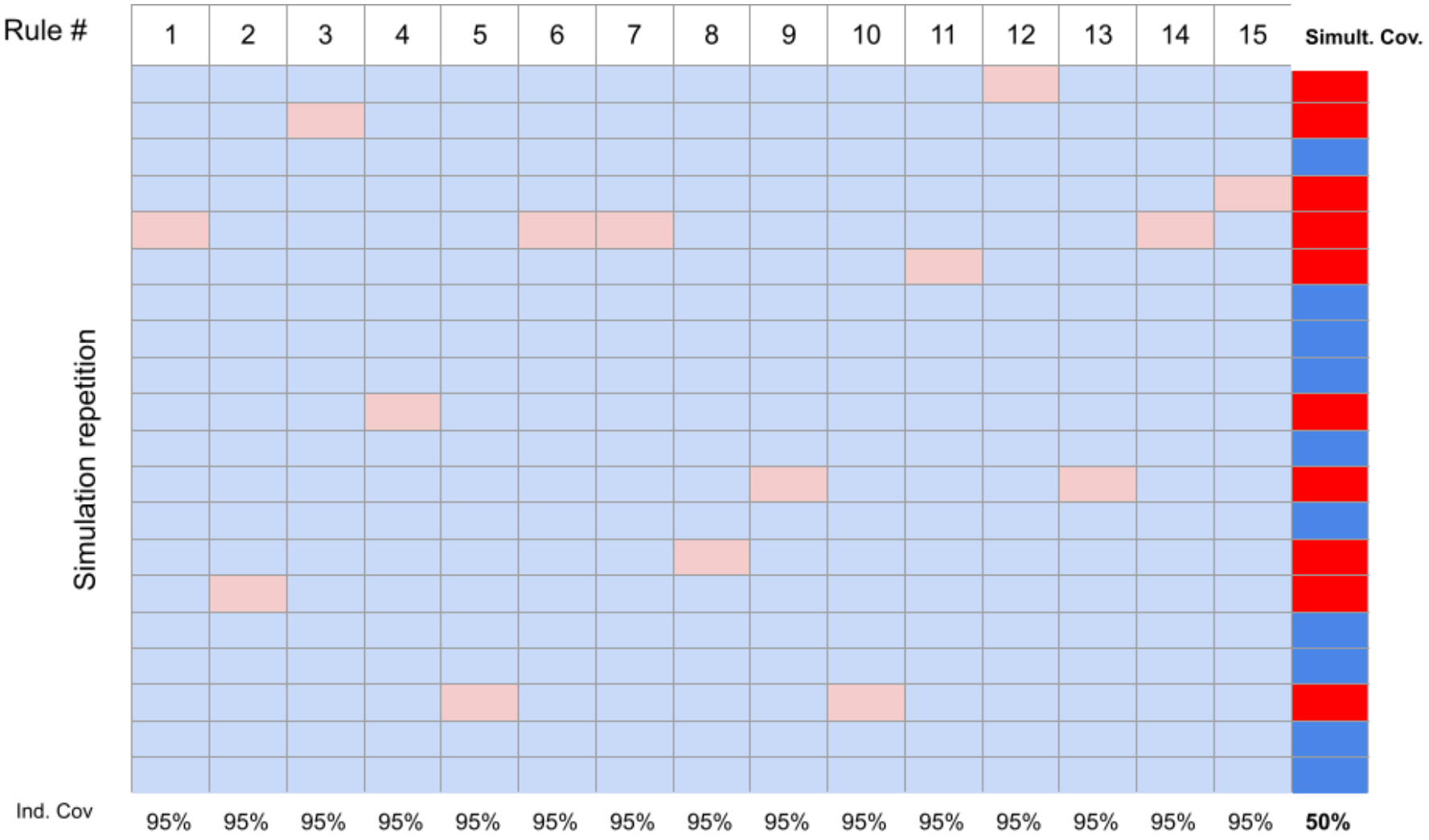
Individual Inference...



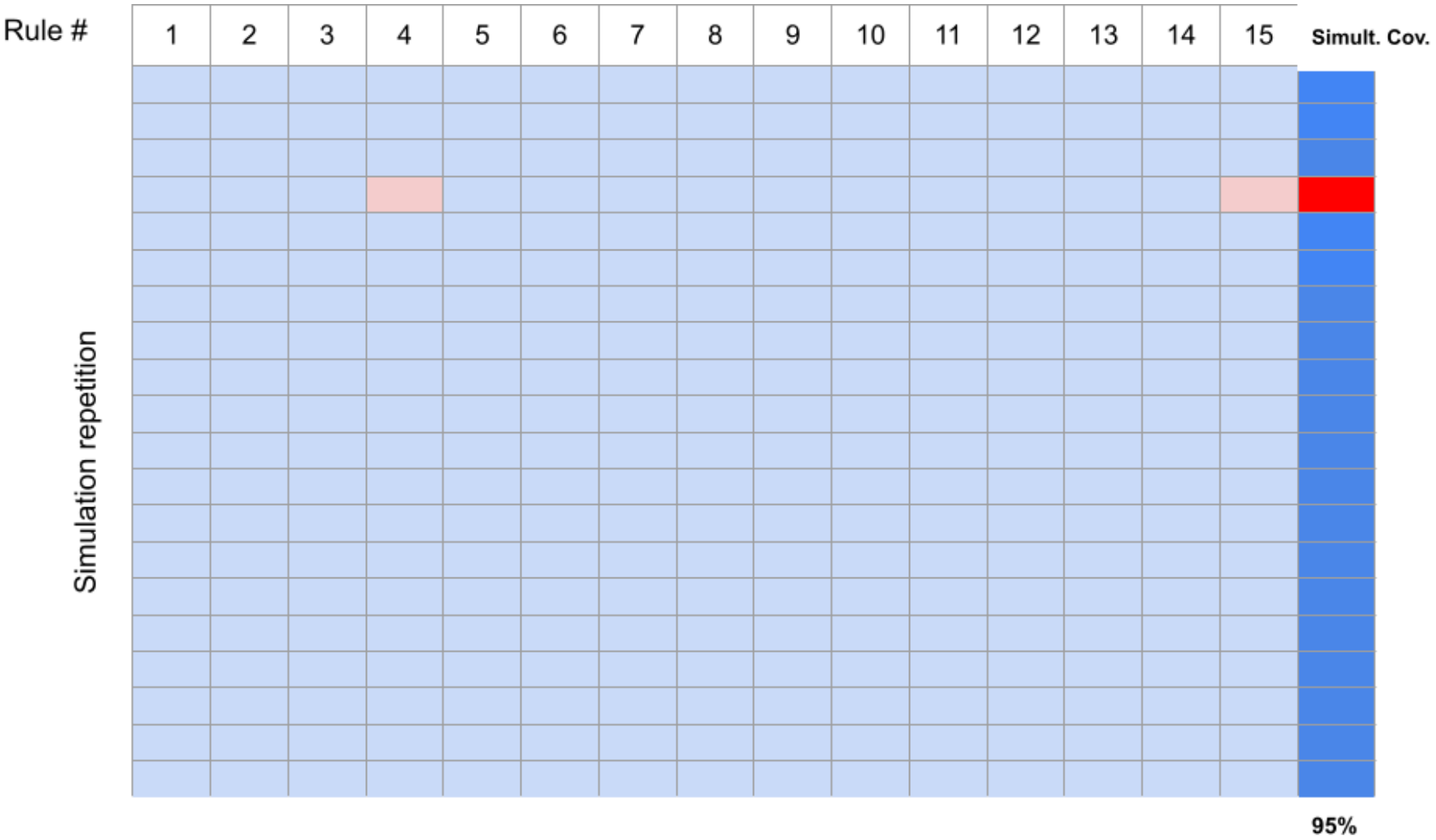
Individual Inference...



Individual Inference...



...vs. Simultaneous Inference



Simultaneous Inference for all Embedded Regimes

Procedure for simultaneous confidence intervals:

1. Let $\rho = Corr(IC(P_0))$
2. Generate random $Z \sim \mathcal{N}(0, \rho)$
3. Get 95th quantile of $\max_j |Z(j)|$, call this $q_{0.95}$
4. Then, a 95% CI for one of the SMART's embedded regimes $d^{(j)}$, $j = 1, ..., D$ is:

$$\hat{\Psi}_{d^{(j)}}(P_n) \pm q_{0.95} \frac{\hat{\sigma}_j}{\sqrt{n}}$$

Pause

Pause

Outline

Simulations - ADAPT-R

- Outcome-blind simulations to evaluate estimator before implementation on real data
  - Specifically, evaluation of:
    - Covariate adjustment for efficiency without overfitting
    - Simultaneous confidence interval-based inference for multiple testing
- Procedure for outcome-blind simulations:
  - Re-sample, with replacement, from empirical distributions of $X(1)$, and $X(2)$
  - Generate $A(1)$ and $A(2)$:
    - $A(1) \sim Multinom(1, p_{SMS} = p_{Voucher} = p_{SOC} = 1/3)$
    - If $L(1) = 1$,
      $A(2) \sim Multinom(1, p_{SMS+Voucher} = p_{Nav.} = p_{SOC} = 1/3)$
    - If $L(1) = 0$ and $A(1) \in \{SMS, Voucher\}$,
      $A(2) \sim Bern(p = 1/2)$
    - If $L(1) = 0$ and $A(1) = SOC$, $A(2) = Continue$
  - $Y \sim Bern(p = Q(X(1), A(1), X(2), A(2)))$

Outline

Outline

Example # 1

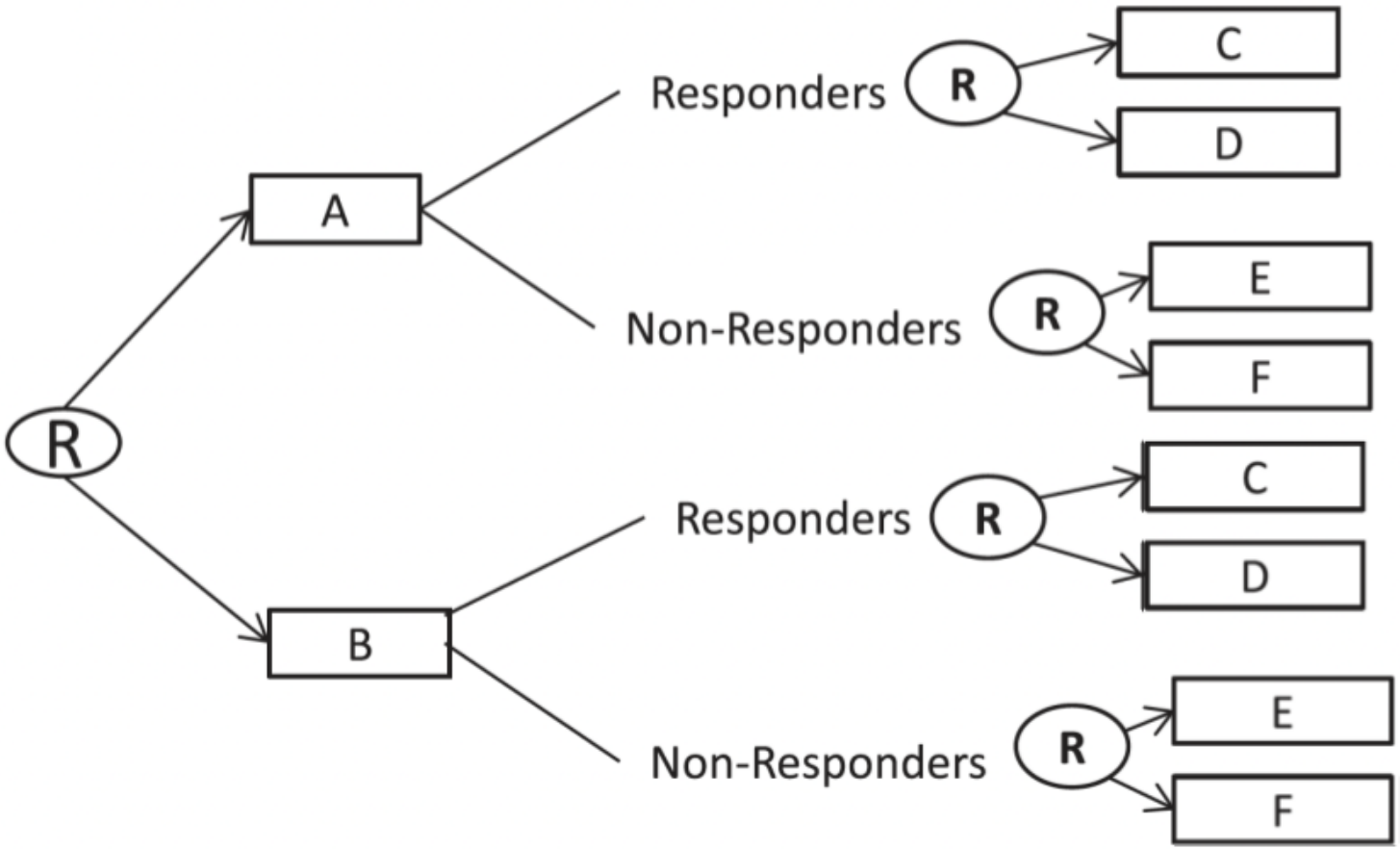


Figure 1: SMART in which administration of second treatment depends on an **intermediate covariate**.

Example # 2

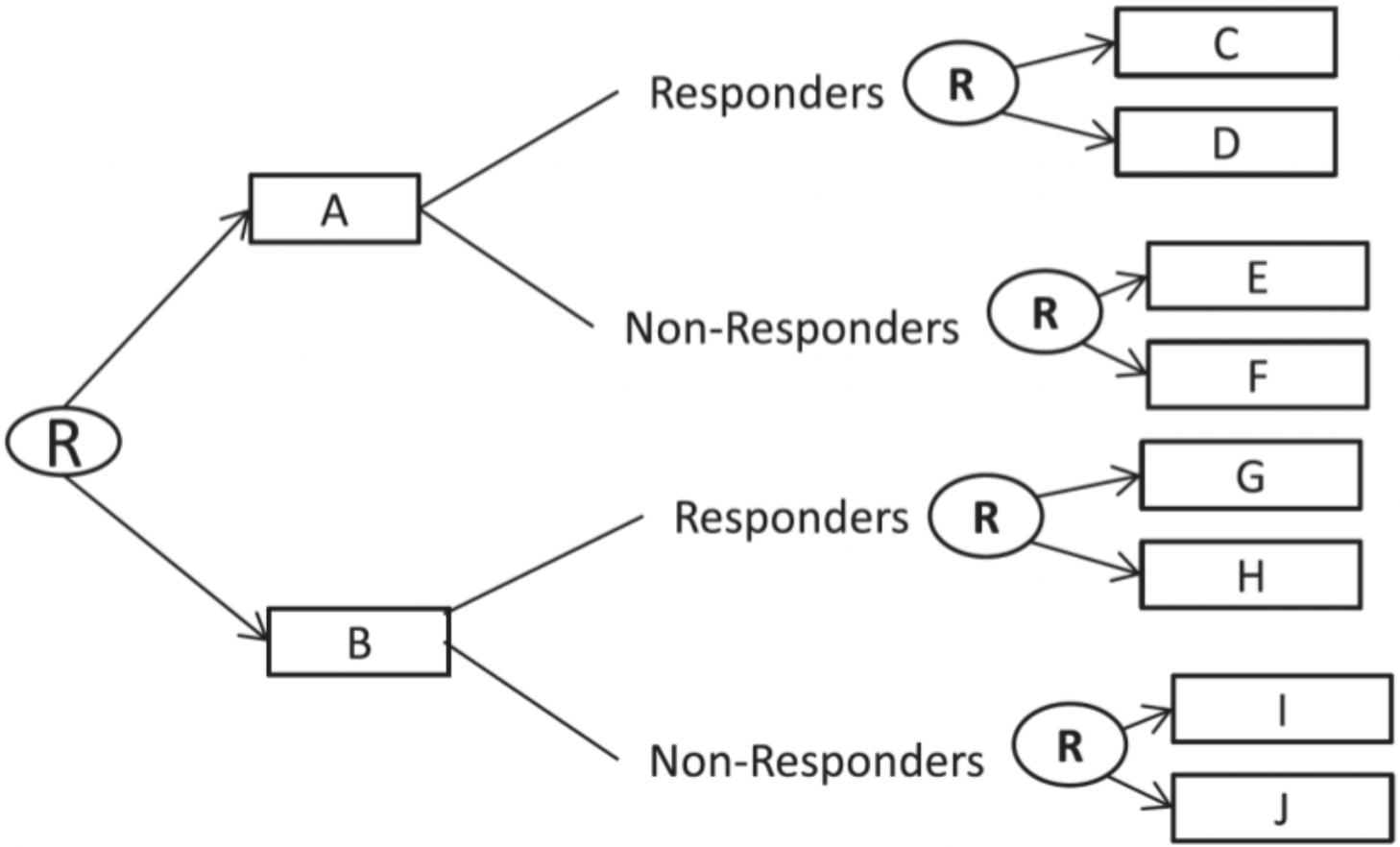


Figure 2: SMART in which administration of second treatment depends on **an intermediate covariate and prior treatment**.

Example # 3

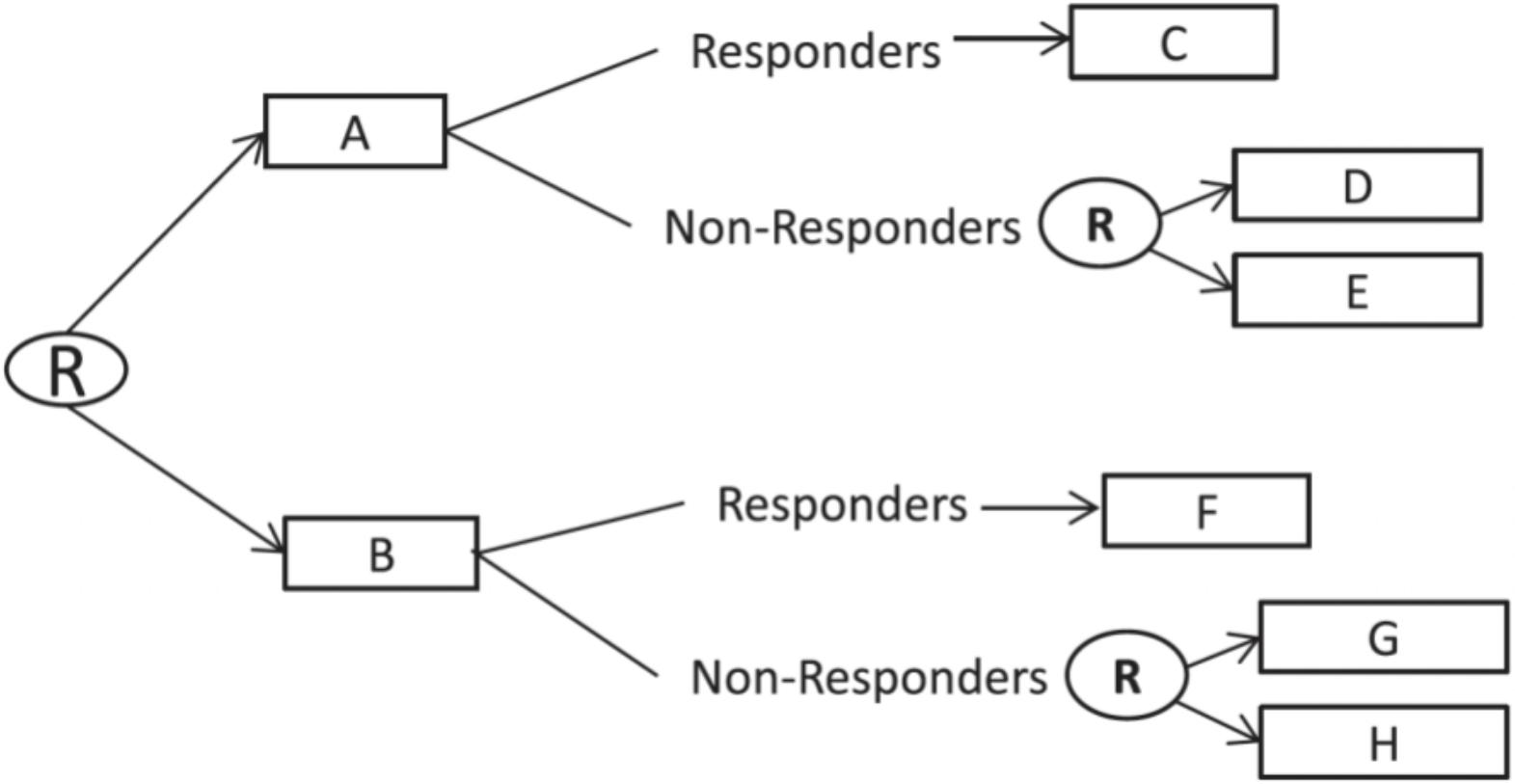


Figure 3: SMART in which administration of second treatment depends **an intermediate covariate and prior treatment...and randomness for non-responders, no randomness for responders**.

Example # 4

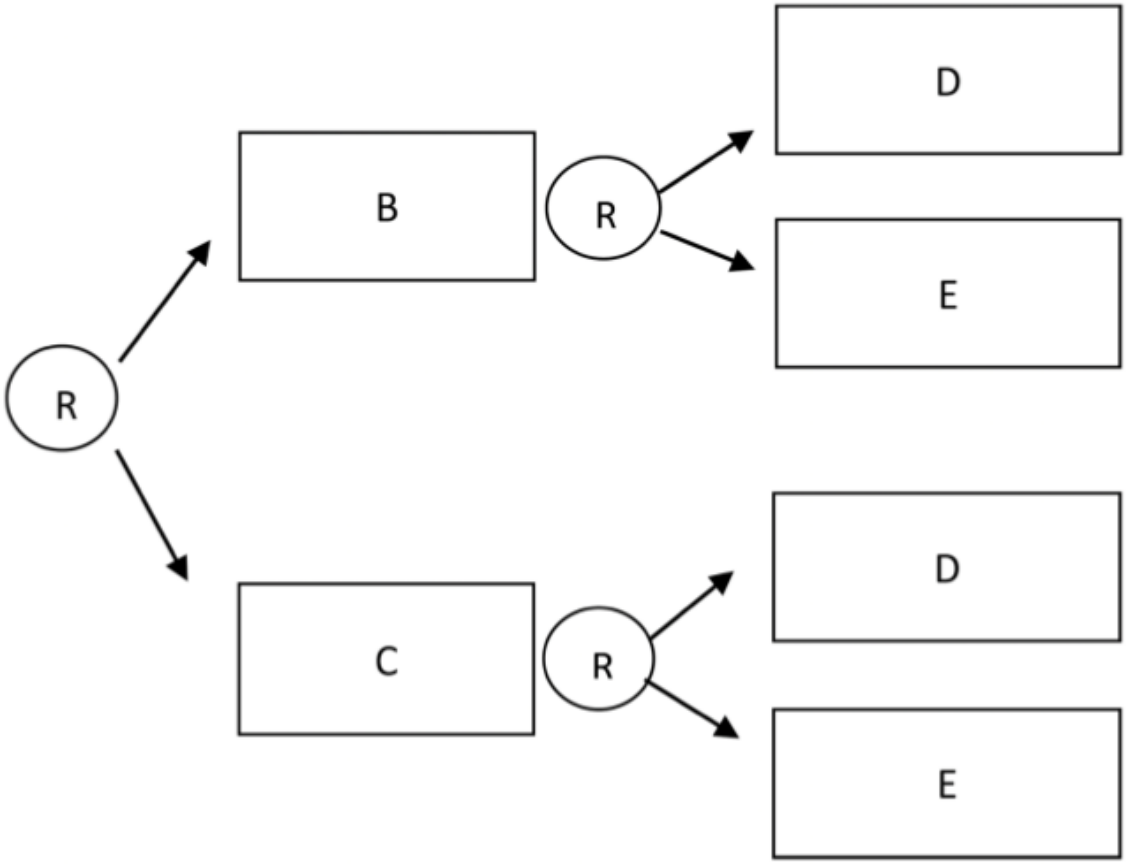
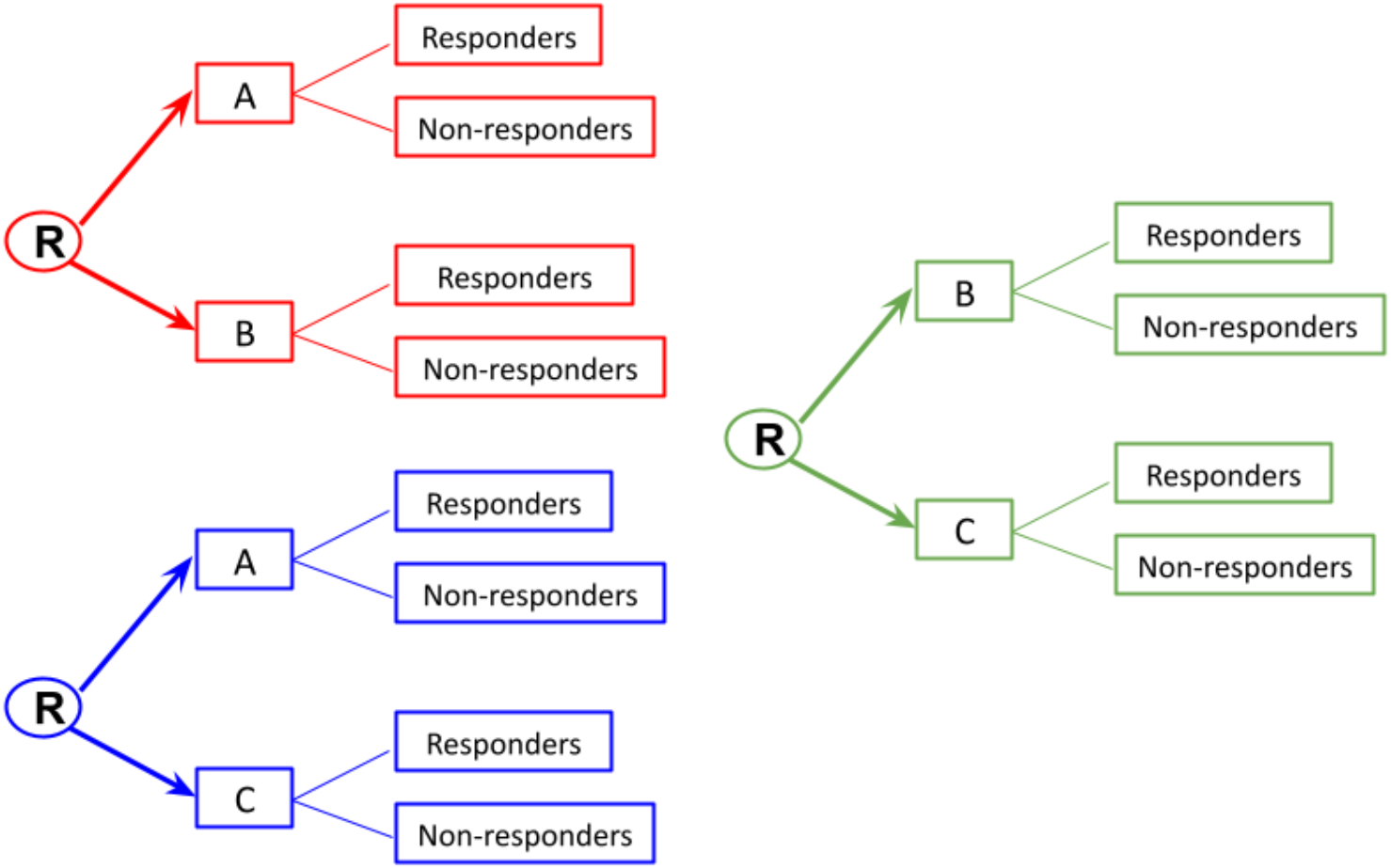


Figure 4: SMART in which whether to re-randomize depends on **no tailoring variables**.

Outline

SMART vs. Separate, One-stage Trials

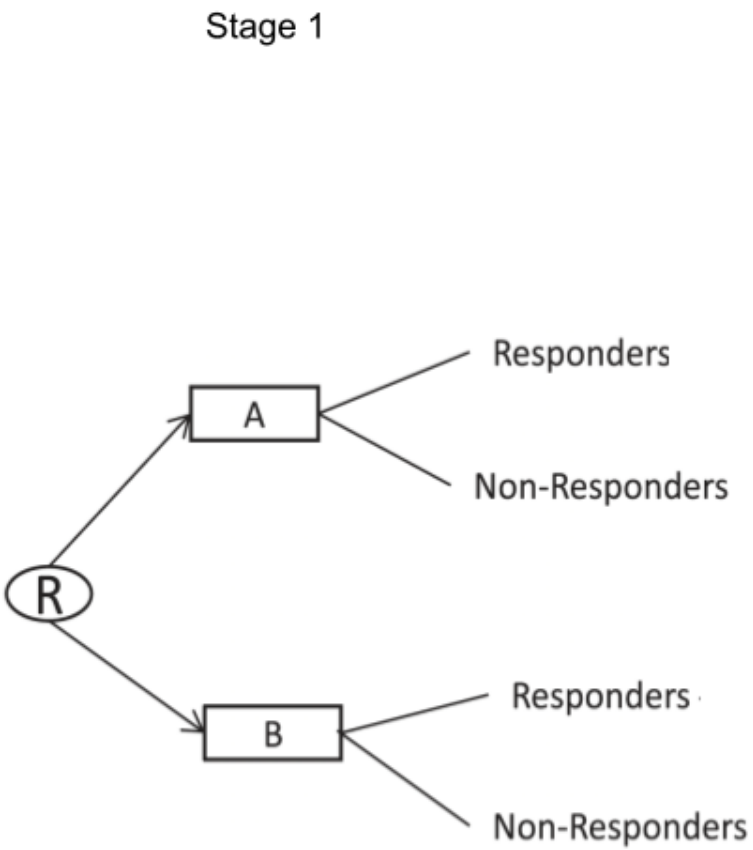


SMART vs. Separate, One-stage Trials

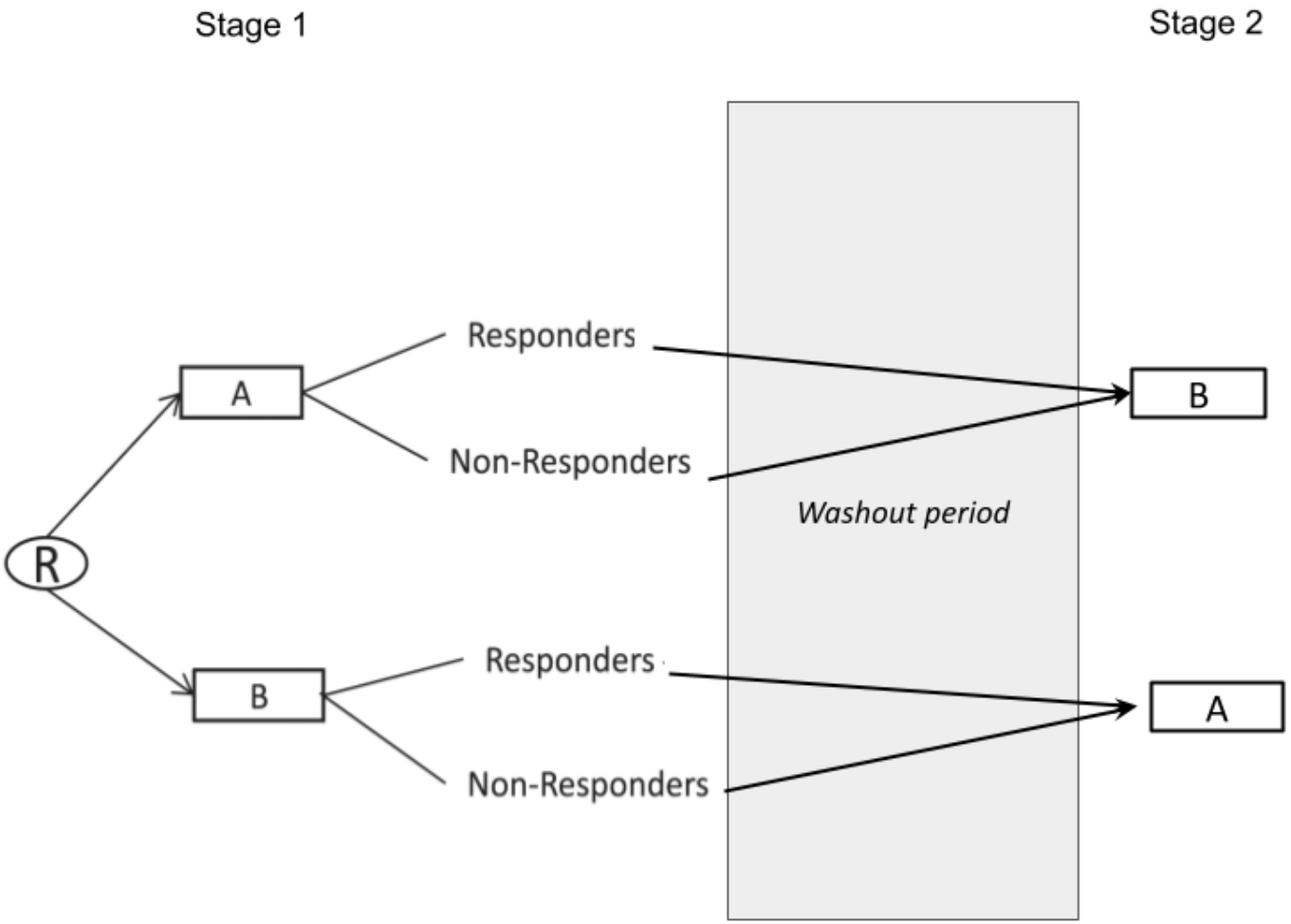
- Do not gather information on the same participant over time $\implies$ can only evaluate point-treatment effects (i.e., myopic results)
  - vs SMART: follows the same individuals throughout the trial $\implies$ can evaluate dynamic treatment regimes in the way we have defined them (i.e., a function of a participants' observed past)
- Different trials may (probably) have samples from distinct, homogenous populations, so, in general, must be careful when combining results from separate trials
  - vs SMART: want to take advantage of heterogeneity, so may be generalizable to a wider group of individuals

Outline

SMART vs. Crossover Design



SMART vs. Crossover Design

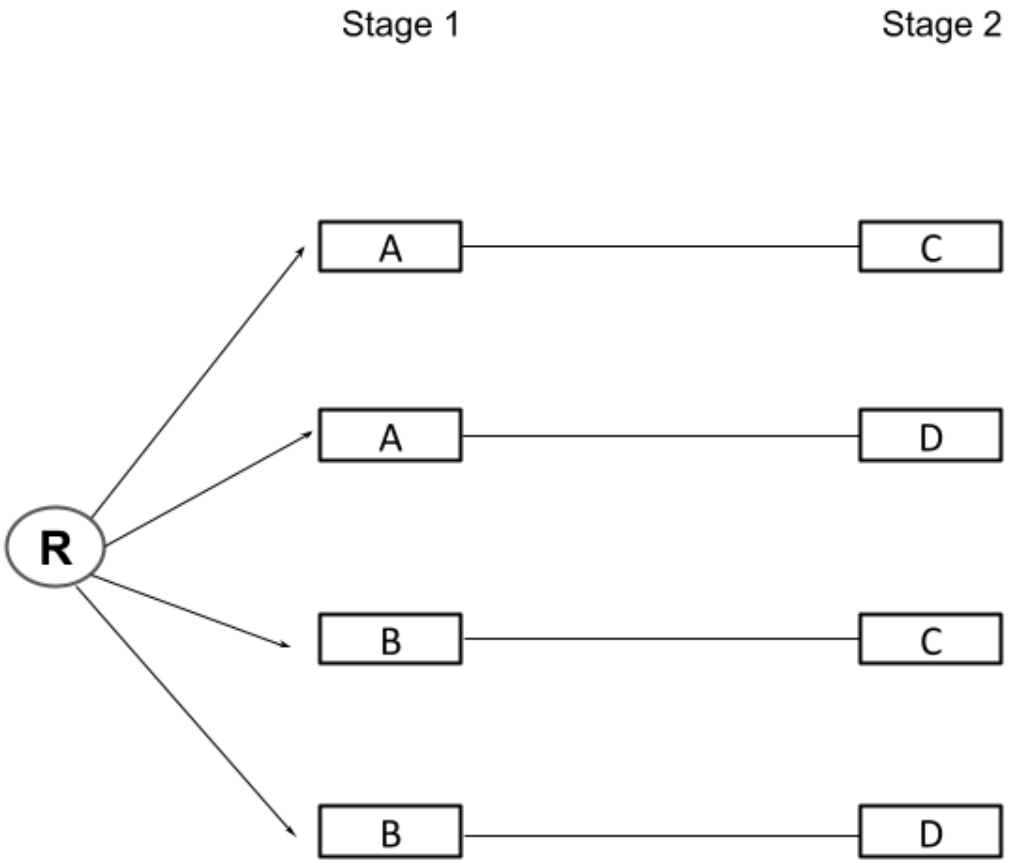


SMART vs. Crossover Design

- Crossover trials involve giving two or more treatments to the same group of individuals with a washout period between each treatment
  - vs SMART: does not require a washout period because they are often interested in responses to those treatments
- Crossover designs deterministically assign as second treatment the opposite of first treatment
  - vs SMART: second treatment is often a function of response to first treatment

Outline

SMART vs. Factorial Design

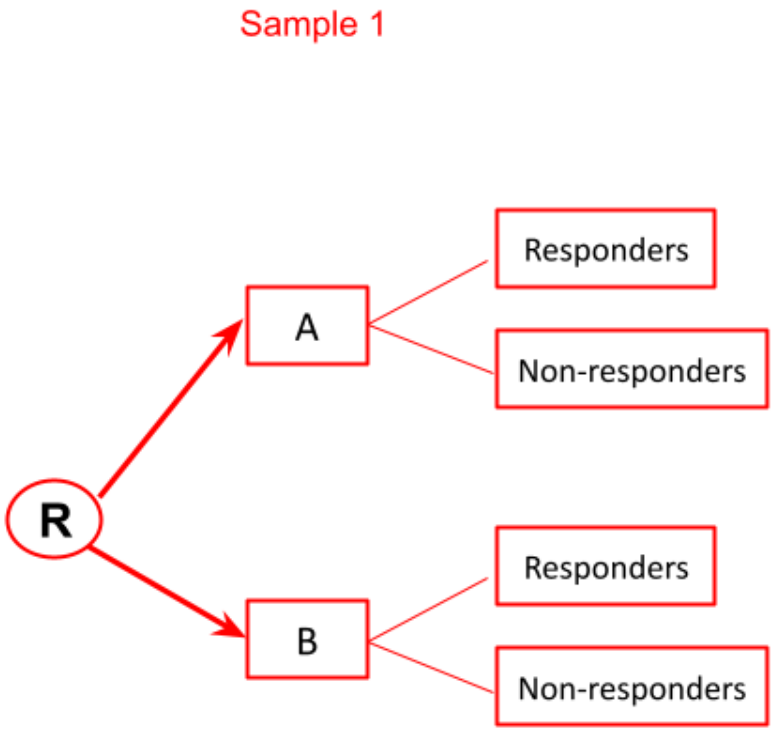


SMART vs. Factorial Design

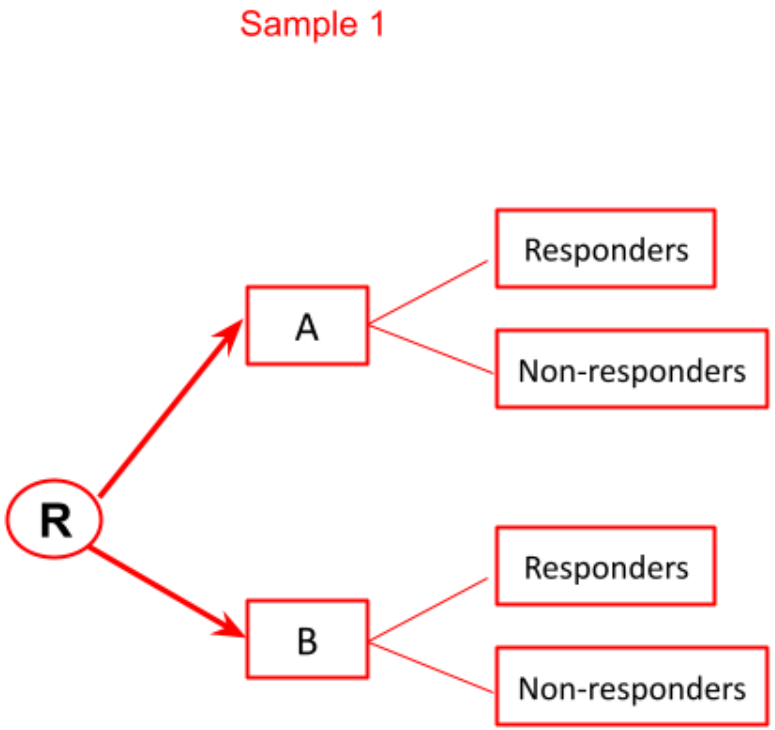
- Factorial trials randomize to a specific sequence of treatments (often given simultaneously)
  - vs SMART: treatment allocation in a SMART depends on intermediate outcomes and are sequential rather than simultaneous
- A SMART may be thought of as a version of a sequential factorial design tailored to intermediate response

Outline

SMART vs. Adaptive Design



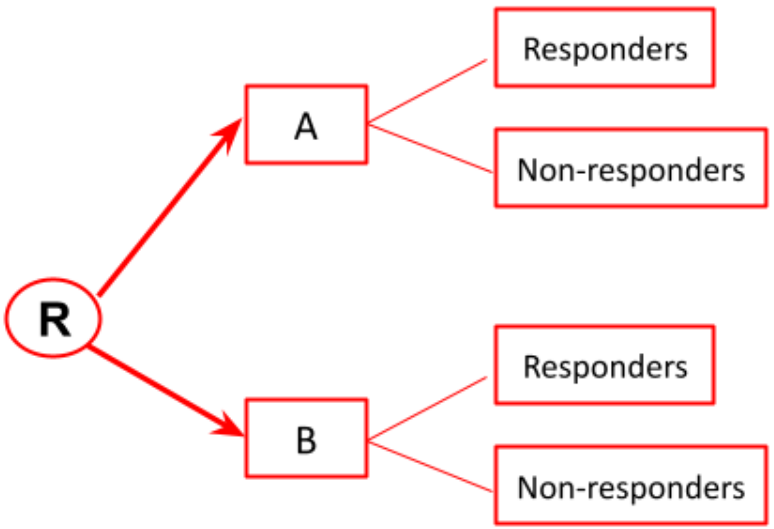
SMART vs. Adaptive Design



SMART vs. Adaptive Design

Sample 1

Sample 2



How to collect data, given Sample 1?

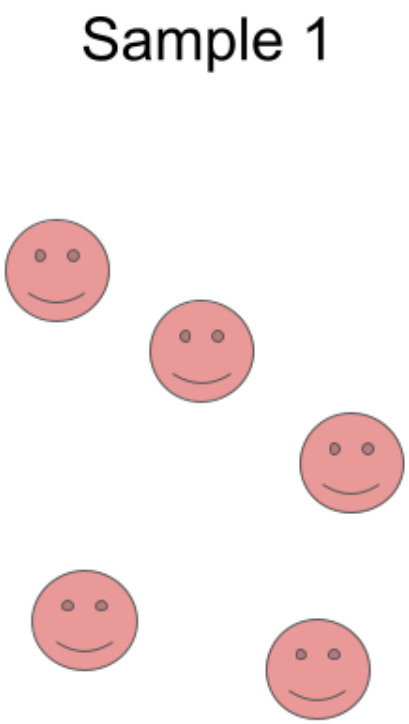
SMART vs. Adaptive Design

****Adaptive designs and SMARTs are often confused for one another!**

- Adaptive designs modify an operational characteristic of the trial while it is ongoing based on collected data
  - vs SMART: the trial design is fixed
- Trial feature changes for future individuals based on past individuals, i.e., the adaptive behavior is *between* individuals
  - vs SMART: the same individual may change treatment based on his or her own information, not on all the information from everyone in the trial up to the point of re-randomization, i.e., adaptation occurs *within* individuals

SMART vs. Adaptive Design

Adaptive Design: Sample size re-estimation (e.g., adjust sample size to ensure desired power)



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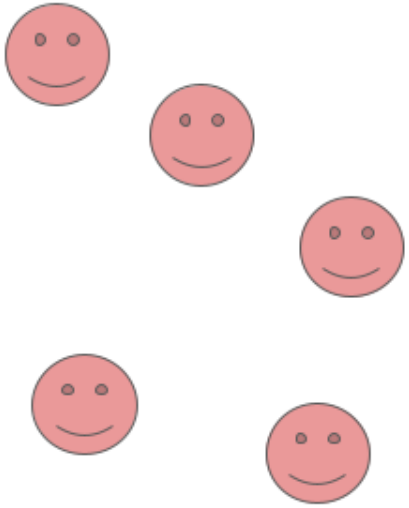

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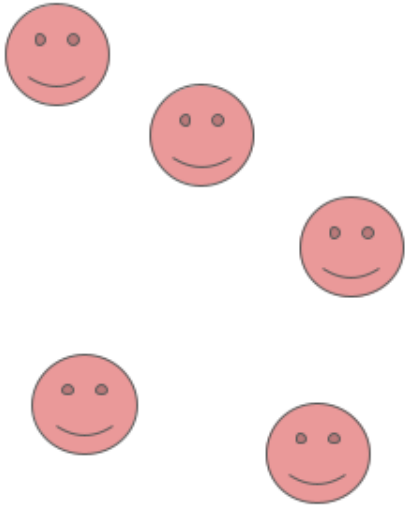
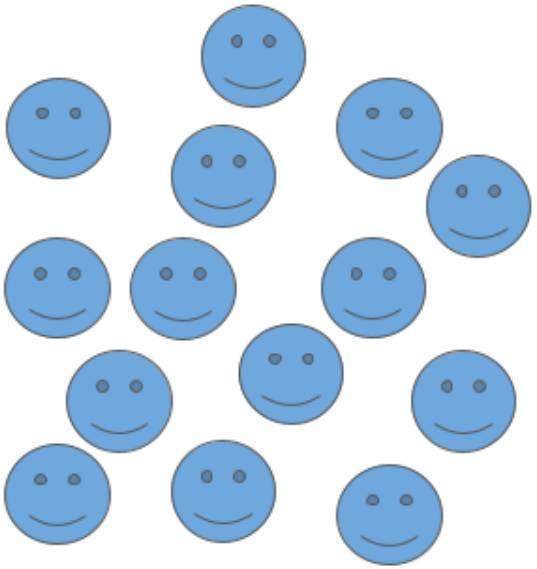
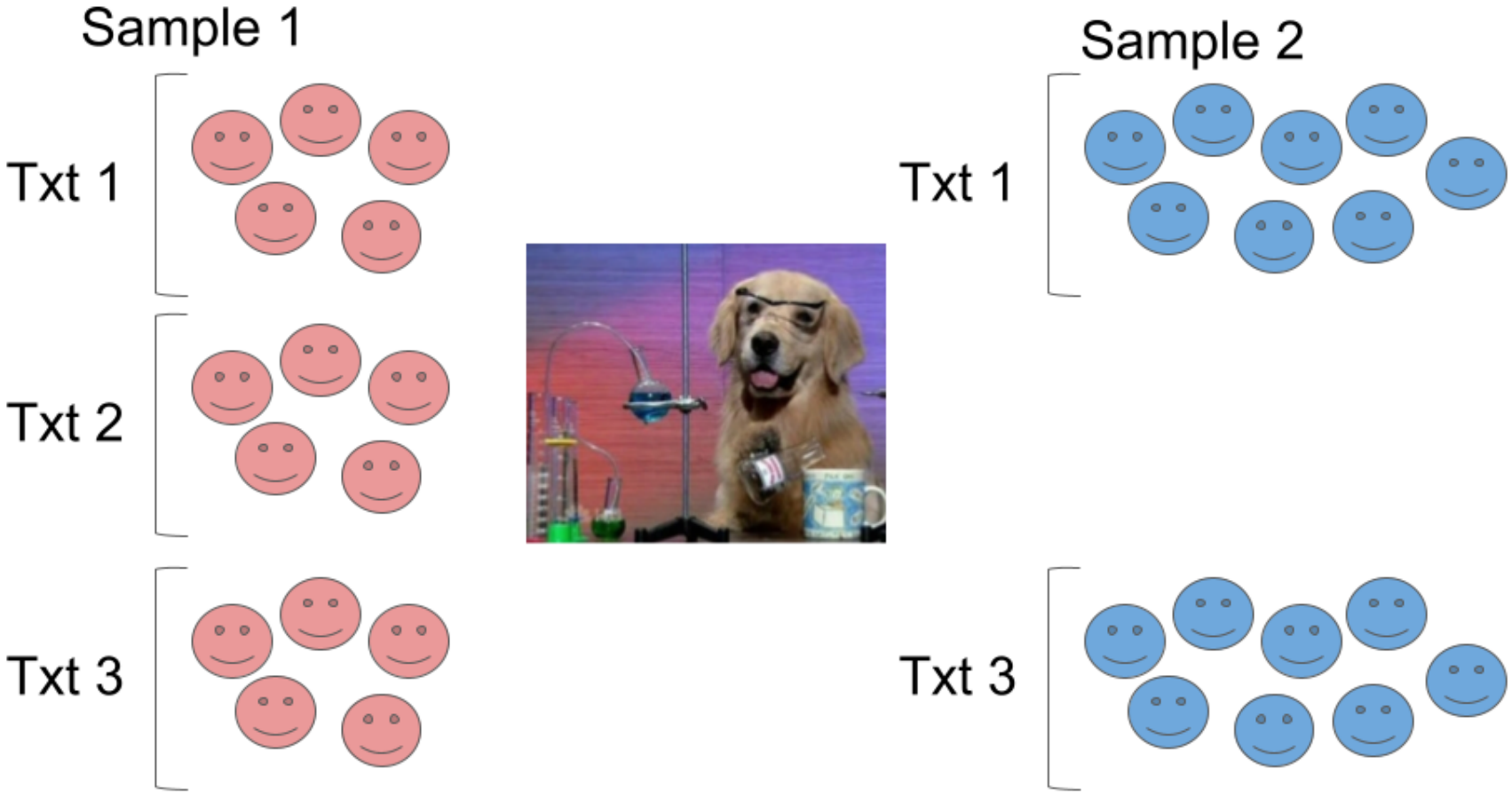


Sample 2



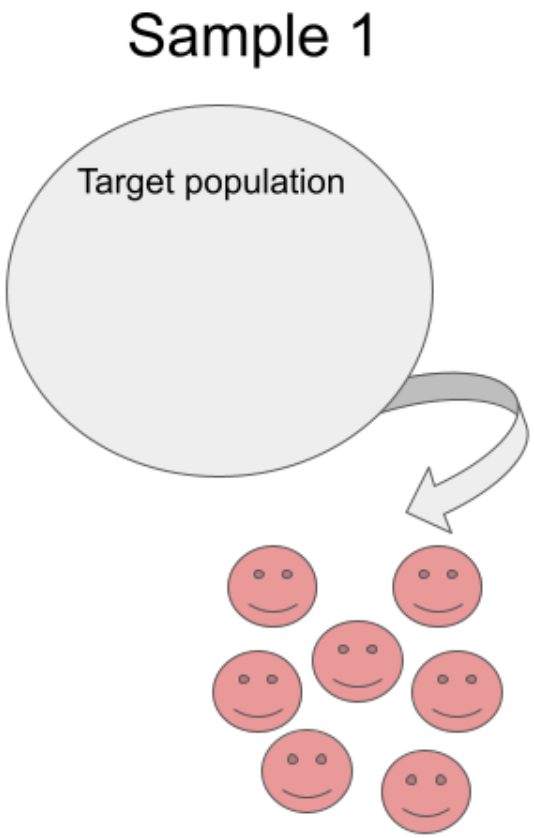
SMART vs. Adaptive Design

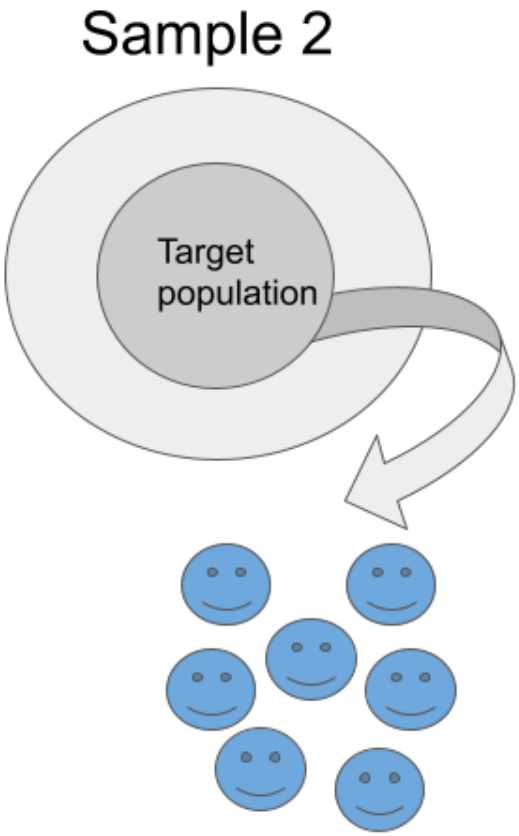
Adaptive Design: Drop inferior arms



SMART vs. Adaptive Design

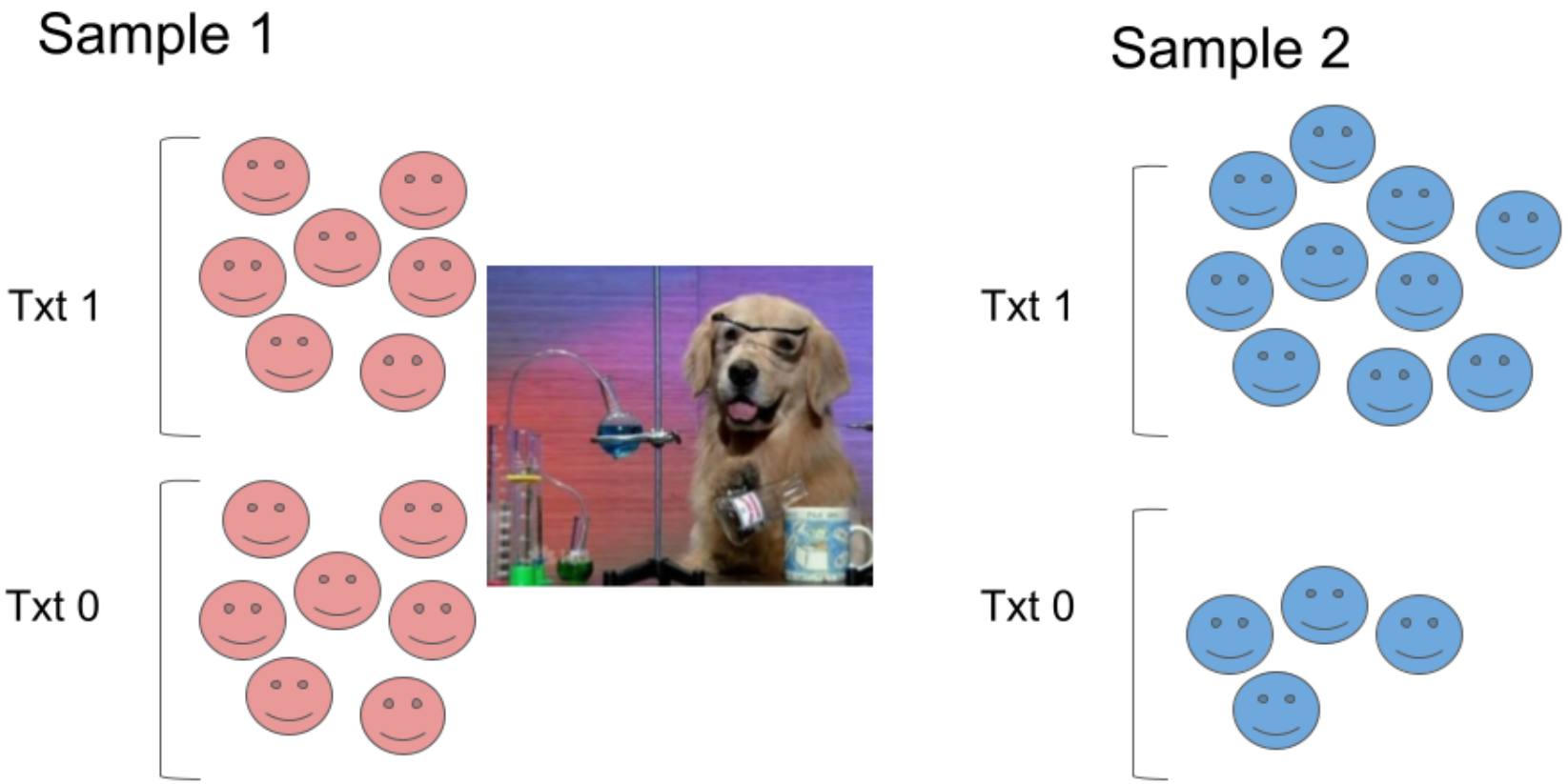
Adaptive Design: Shift in target population (e.g., changes in inclusion/exclusion criteria)





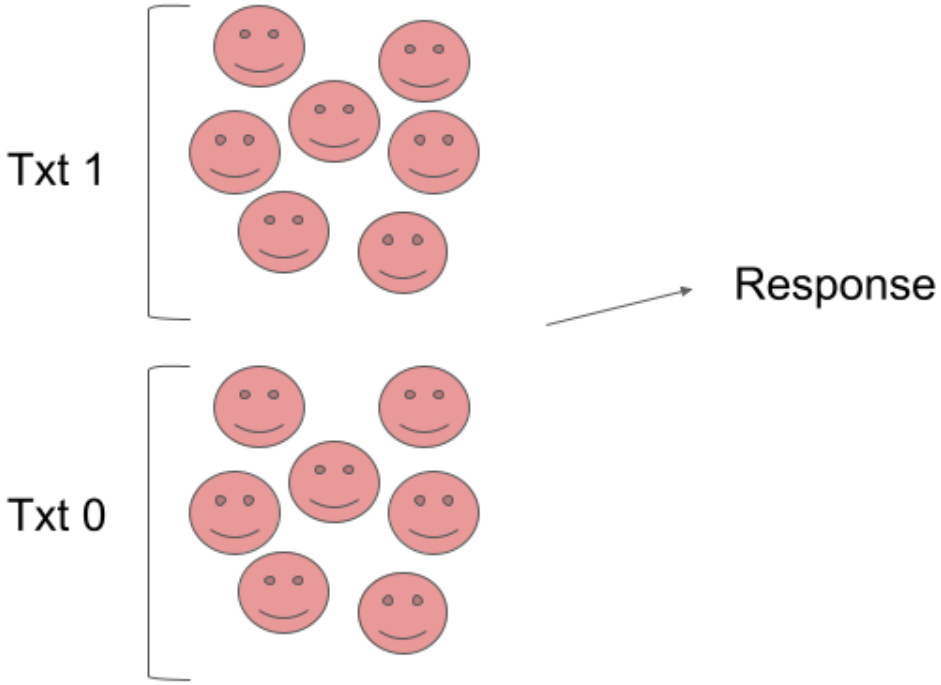
SMART vs. Adaptive Design

Adaptive Design: Adaptive randomization - updating treatment assignment probabilities based on accrued data



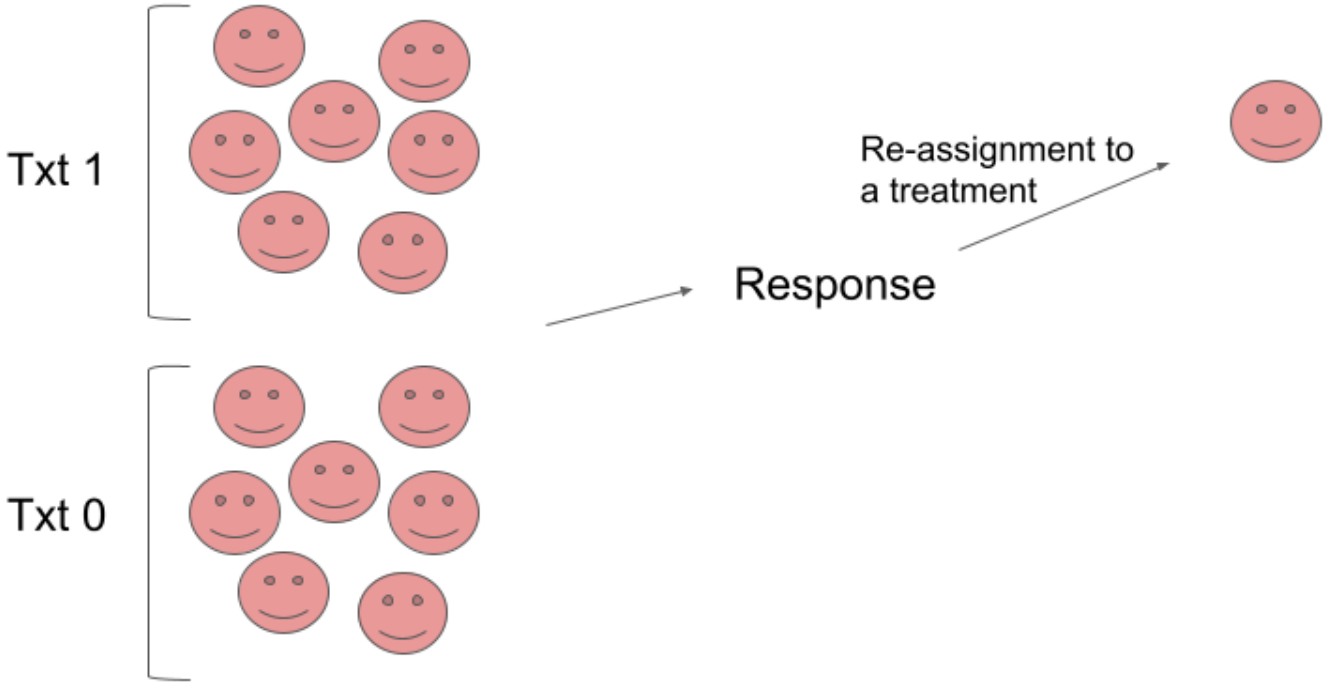
SMART vs. Adaptive Design

vs. a SMART...



SMART vs. Adaptive Design

vs. a SMART...



Outline

Powering a SMART

Before embarking on a power calculation for a SMART, one must define specific aims of the trial

Defining Trial Objectives/Aims

Possible aims are closely aligned with possible causal questions. From Kidwell, Ch. 2 Kosorok & Moodie book:

- What is the best first-stage treatment?
- What is the best second-stage treatment for (non)responders to a particular first-stage treatment?
- Do expected outcomes significantly differ between two or more DTRs?
- For a specific DTR, can we improve individual outcomes by further tailoring treatment by baseline or time-varying characteristics?

Defining Trial Objectives/Aims

From Kidwell, Ch. 2 Kosorok & Moodie book:

- What is the best first-stage treatment?
  - "Typical" methods for powering main effects (e.g., when powering an RCT)
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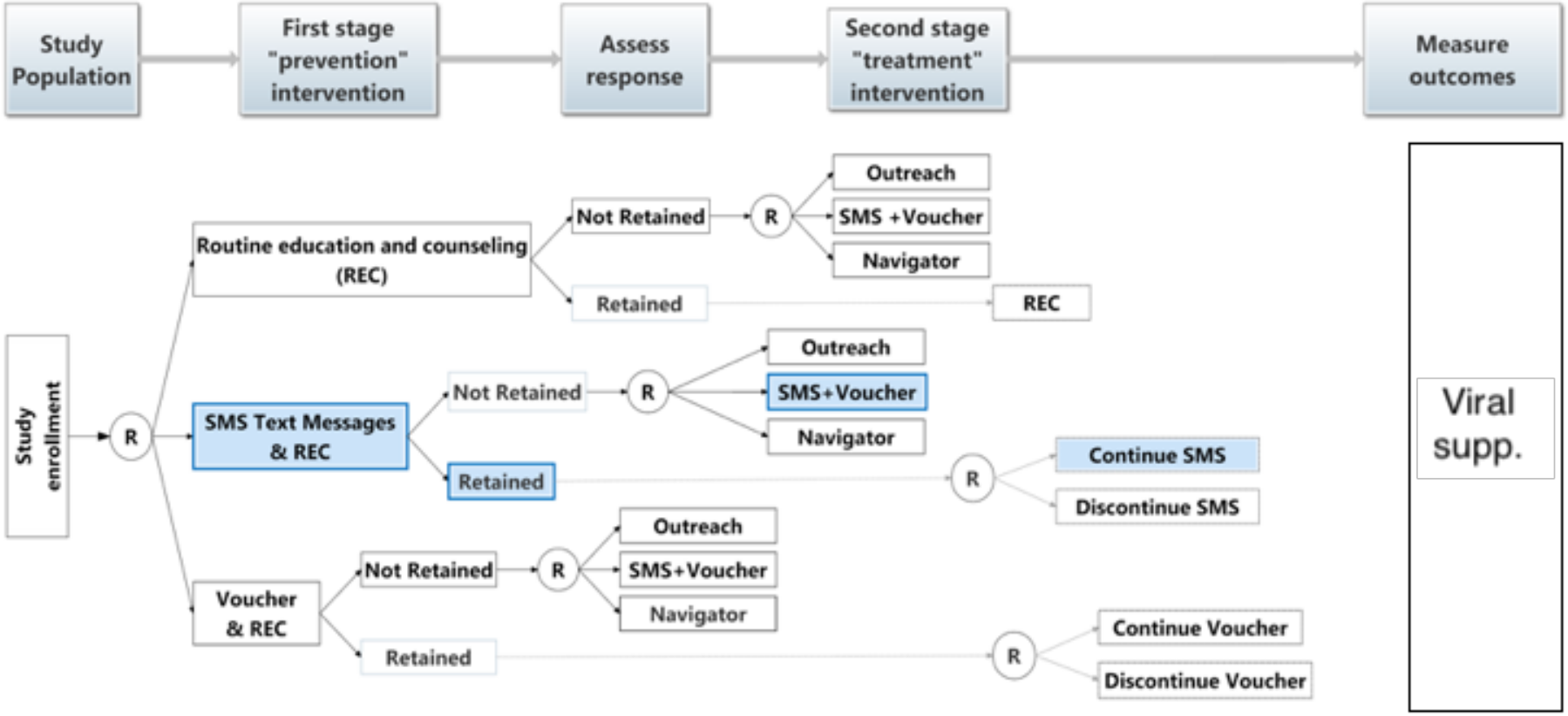
- What is the best second-stage treatment for (non)responders to a particular first-stage treatment?
  - "Typical" methods for powering main effects (e.g., when powering an RCT)
- Do expected outcomes significantly differ between two or more DTRs?
  - Sample size calculators exist (see Kosorok & Moodie book)
  - Can also do this via simulations (e.g., ADAPT-R)
- For a specific DTR, can we improve individual outcomes by further tailoring treatment by baseline or time-varying characteristics?
  - Likely an exploratory aim
  - Complex due to the non-regularity of DTR estimators
    - See Rose, Eric J., et al. 2019 "Sample size calculations for SMARTs."

Recall ADAPT-R Design



Specific Aims ADAPT-R

From Petersen & Geng ADAPT-R R01 Application:

- Aim 1: Assess the comparative effectiveness of interventions to prevent lapses in retention.
  - Compare overall visit adherence over two years between the standard of care, SMS, and voucher arms.
- Aim 2: Assess the effectiveness of interventions to re-engage patients with early lapse in retention.
  - Compare visit adherence between the outreach, SMS + voucher, and navigator arms, pooled across first stage interventions.
- Aim 3: Assess the effectiveness and cost-effectiveness of sequential prevention-reengagement strategies for retention.
  - Evaluate the effectiveness of the embedded sequential strategies on a combined outcome of survival and viral suppression (for treatment eligible) or in care status (for treatment ineligible) at two years.

Outline