Precision Medicine: Lecture 09
SMART Design & Analysis

Lina Montoya, Michael R. Kosorok,
Nikki L. B. Freeman and Owen E. Leete

Department of Biostatistics
Gillings School of Global Public Health
University of North Carolina at Chapel Hill

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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

Outline

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Recall...

- In precision medicine, we often want to know: who should get which treatment?
  - And at what time?
  - And at what dose?
  - And in what sequence?
  - Etc.
- Further: Is giving treatment in an individualized way better than giving it in a non-individualized way (e.g., giving everyone the same treatment)?
- These are fundamentally causal questions

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- Further: Is giving treatment in an individualized way better than giving it in a non-individualized way (e.g., giving everyone the same treatment)?
- These are fundamentally <u>causal</u> questions
- **What kinds of trials – by design – easily allow for answering these causal questions?**
  - "easily allow for" = by design, satisfy causal assumptions

Sequential Multiple Assignment Randomized Trial (SMART)

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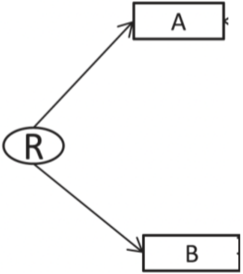
- Multistage trial in which administration of treatment (either random or not) is a function of pre-specified variable(s) measured during the trial
- Said another way: Multistage trial in which participants follow specific dynamic treatment regimes
  - These "specific regimes" are a SMART's **embedded regimes**

Example # 1



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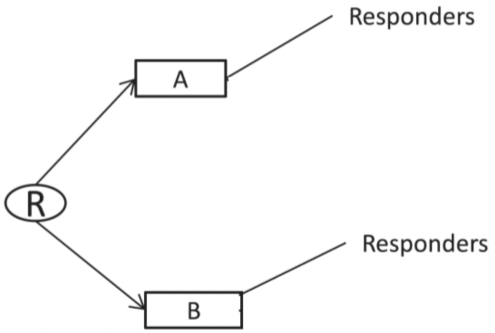

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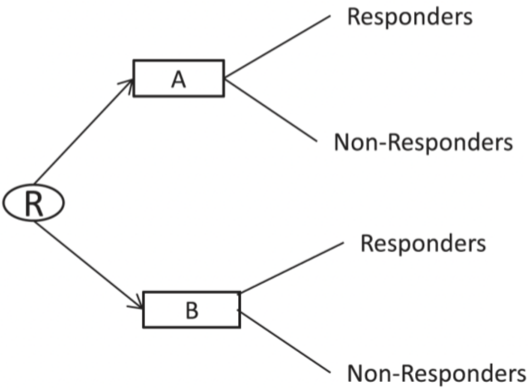

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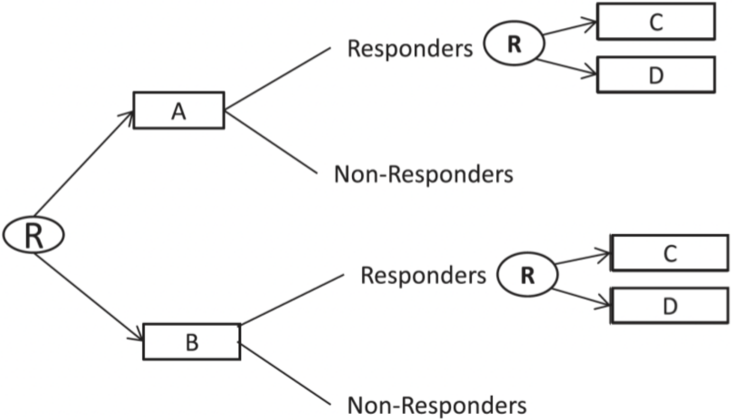
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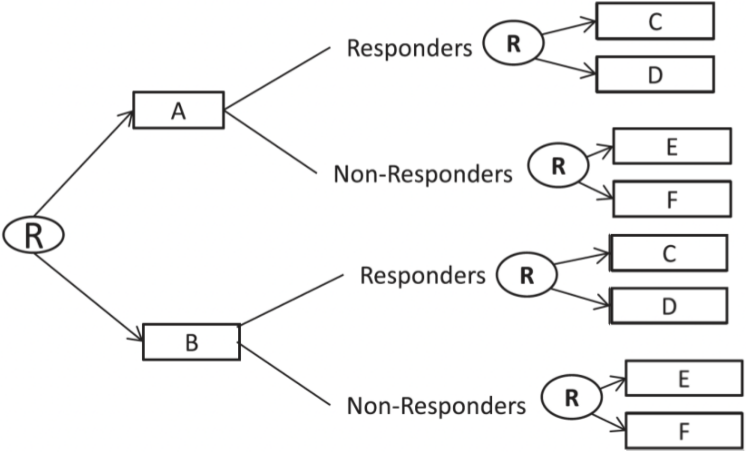
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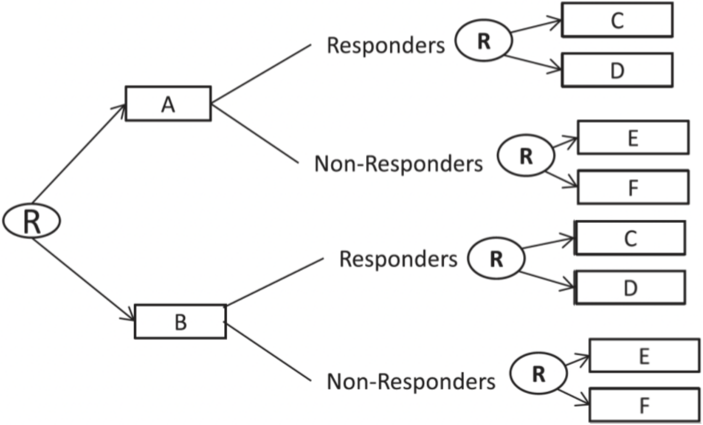
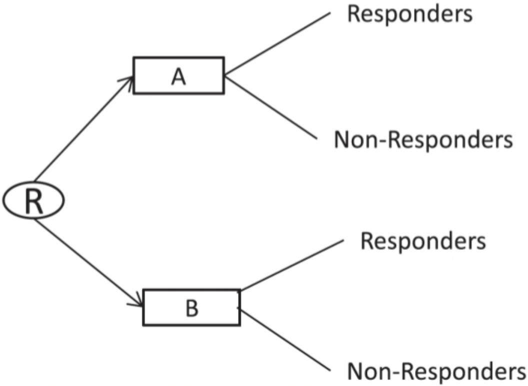


Figure 1: SMART in which administration of second treatment depends on an **intermediate covariate**.

Example # 2



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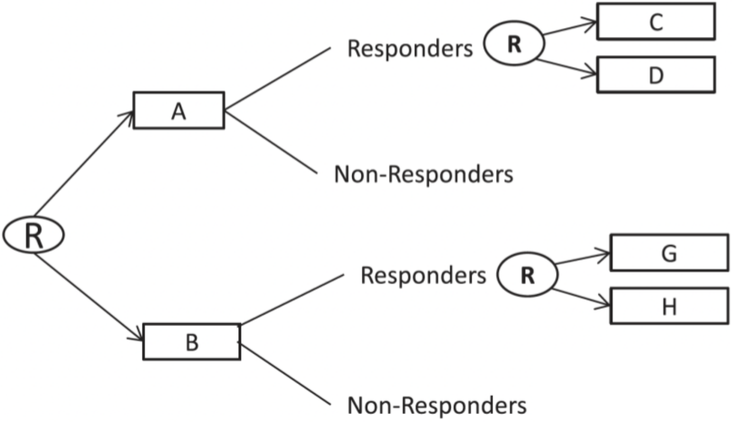
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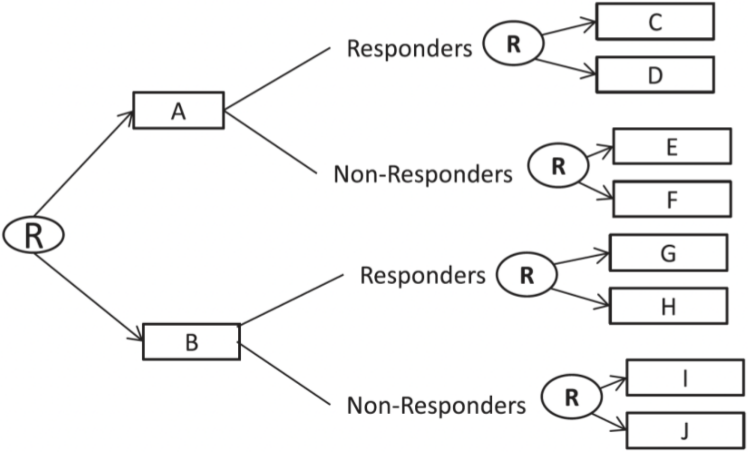
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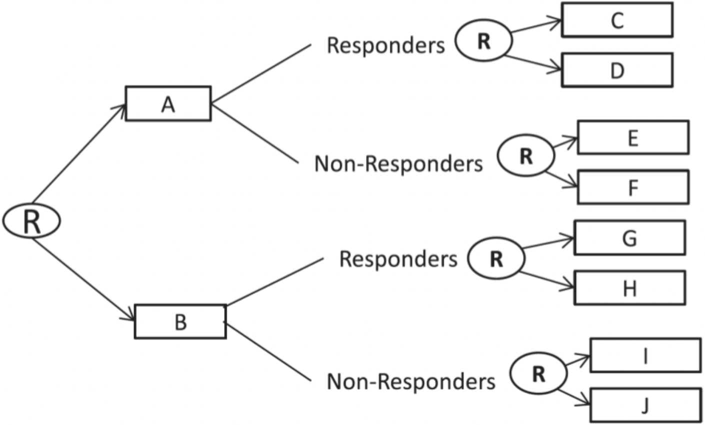


Figure 2: SMART in which administration of second treatment depends on ?

Example # 2

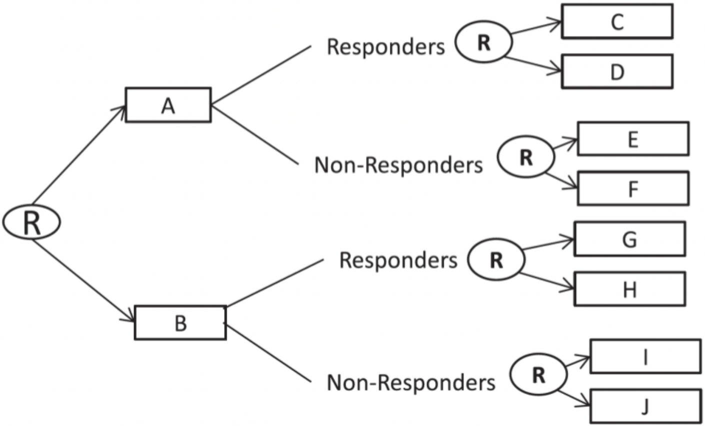
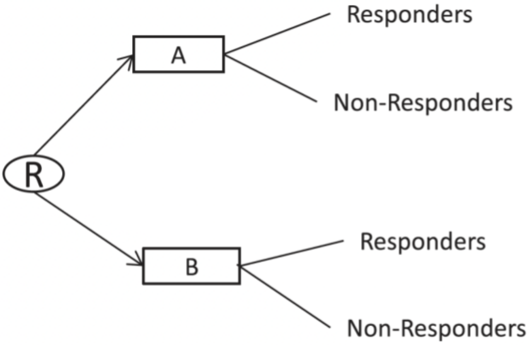
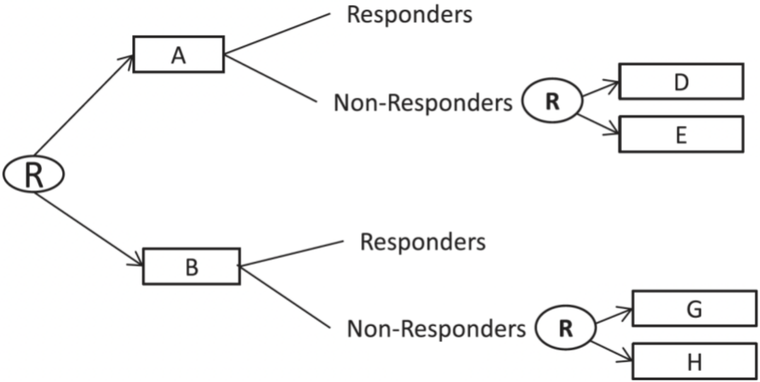


Figure 3: SMART in which administration of second treatment depends on **an intermediate covariate and prior treatment**.

Example # 3



Example # 3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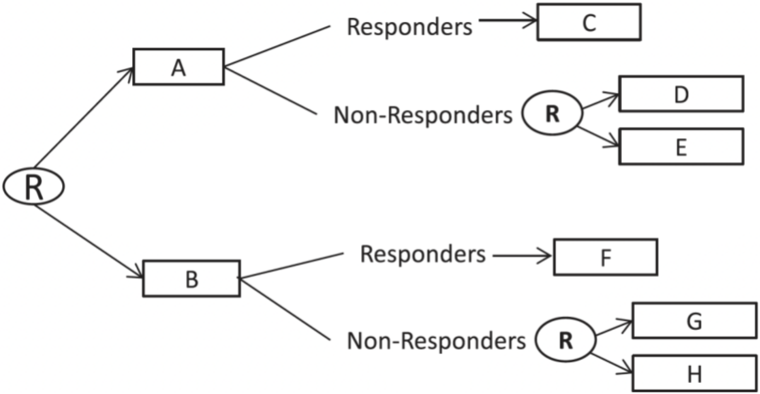

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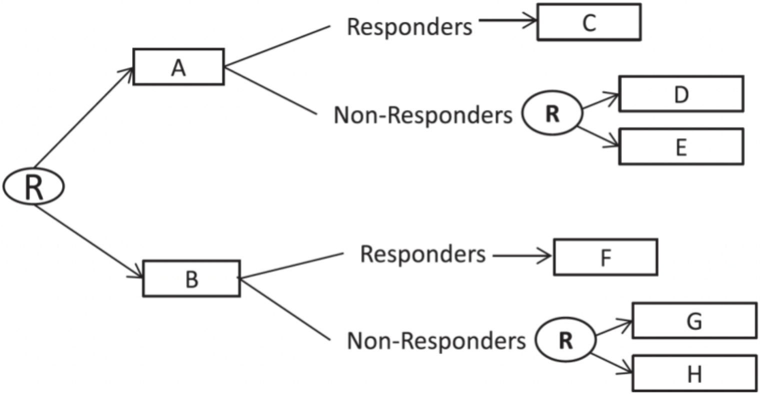


Figure 4: SMART in which administration of second treatment depends on ?

Example # 3

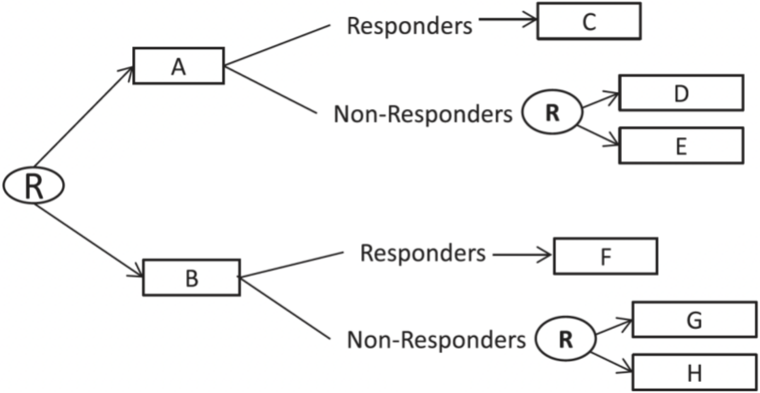
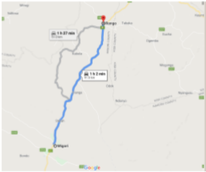


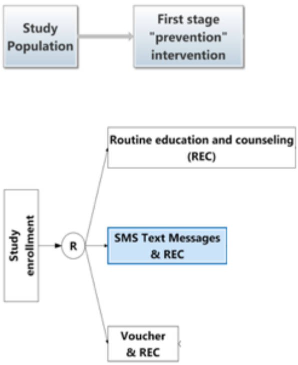
Figure 5: SMART in which administration of second treatment depends **an intermediate covariate and prior treatment...and randomness for non-responders, no randomness for responders**.

Running example - ADAPT-R

- Adaptive Strategies for Preventing and Treating Lapses of Retention in HIV Care (ADAPT-R; PIs: Petersen & Geng)
- Antiretroviral Therapy (ART) potent and effective, but 20-40% of HIV-infected patients in sub-Saharan Africa lost to follow-up within two years after enrolled in care (e.g., Geng, et. al. 2015)
- Many *diverse* barriers to HIV care retention
  - Structural barriers (e.g. transport to clinic)
  - Psychosocial barriers (e.g., stigma)
  - Other (e.g., long clinic waiting times)
- **No "one-size-fits-all" incentive to stay in care**
  - **Want to know which strategy works best for whom**




ADAPT-R Design



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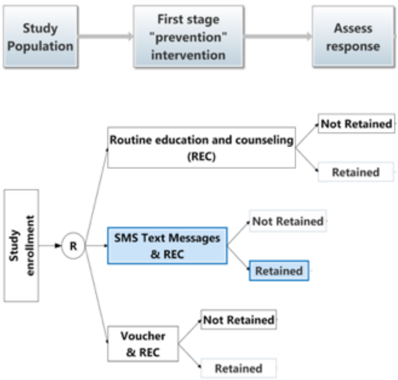

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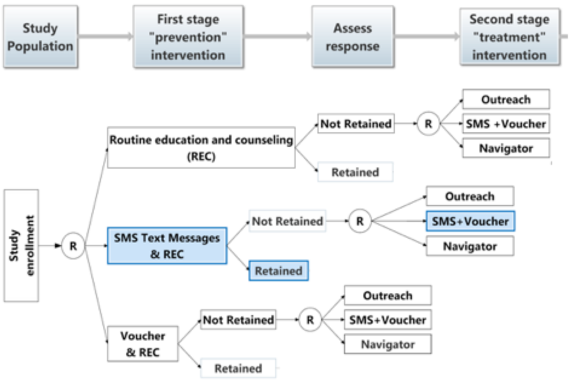

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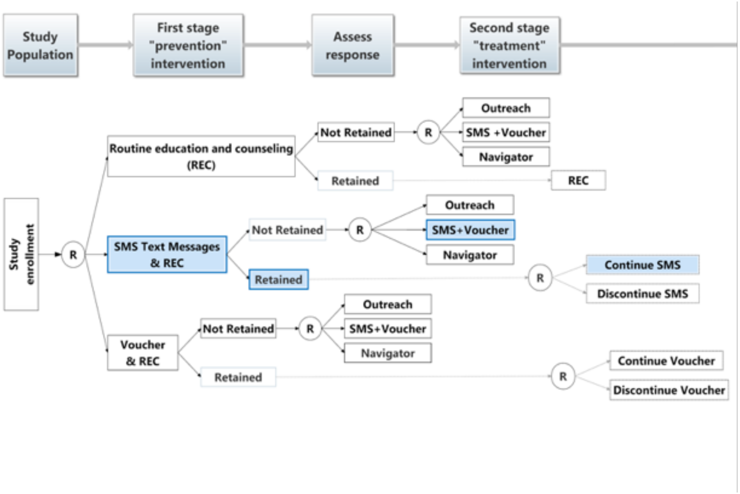

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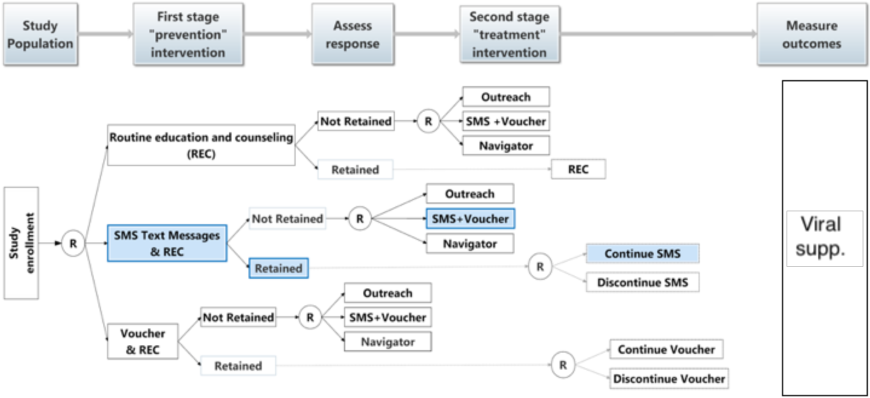

Outline

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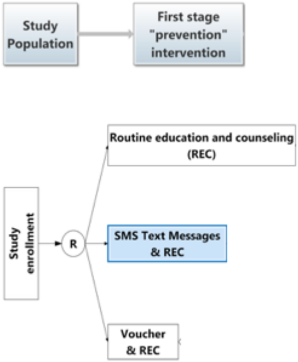
What data come out of a SMART?

Longitudinal data!

In general...

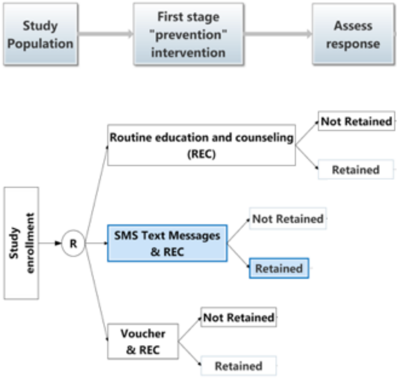
- For a time t, the endogenous variables are
  - Interventions $A(t) \in \mathcal{A}_t$, which could include right-censoring
  - Covariates $X(t)$, which could include baseline covariates and time-varying covariates
  - Outcome Y
- Overbars denote a variable's past history, e.g., $\bar{A}(t) = (A(1), \ldots, A(t))$ and $\bar{X}(t) = (X(1), \ldots, X(t))$
  - $A(0) = X(0) = \emptyset$

ADAPT-R Data



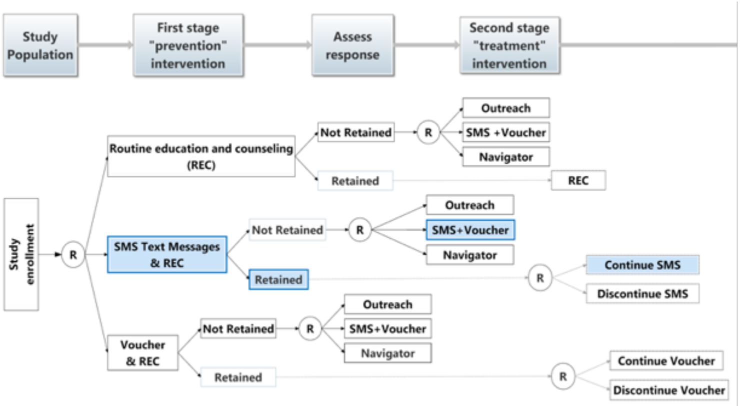
Data collected so far: baseline covariates $X(1)$, Stage 1 intervention $A(1)$

ADAPT-R Data



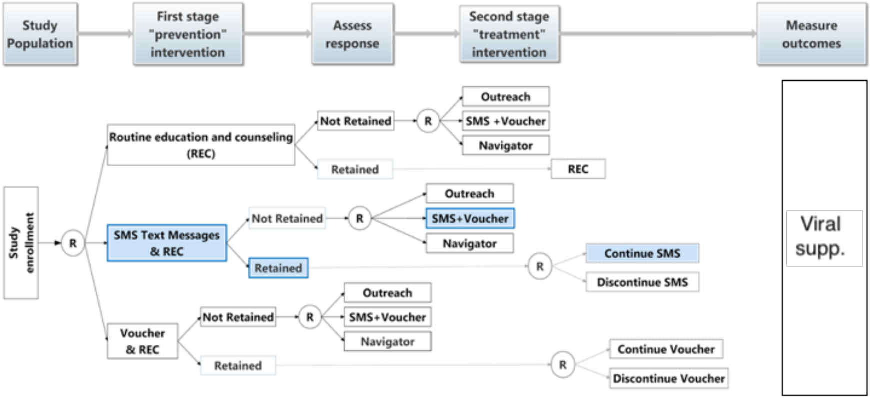
<u>Data collected so far:</u> baseline covariates $X(1)$, Stage 1 intervention $A(1)$, time-varying covariates (incl. first year lapse in care) $X(2)$

ADAPT-R Data



<u>Data collected so far:</u> baseline covariates $X(1)$, Stage 1 intervention $A(1)$, time-varying covariates (incl. first year lapse in care) $X(2)$, Stage 2 intervention $A(2)$

ADAPT-R Data



<u>Data collected so far:</u> baseline covariates $X(1)$, Stage 1 intervention $A(1)$, time-varying covariates (incl. first year lapse in care) $X(2)$, Stage 2 intervention $A(2)$, outcome Y

ADAPT-R Data

Note: $t = 1$ is time of first randomization; $t = 2$ is time of first retention lapse or end of first year

- **X(1)** = baseline covariates (e.g., sex, age, WHO stage, CD4 count, clinic site, etc.)
- **A(1)** = Stage 1 prevention intervention
  - standard of care, SMS text messaging, transportation voucher
- **X(2)** $= (S(2), L(2))$ = time-varying variables
  - $L(2)$ = indicator of lapse in care ($\geq$ 14 days late to a clinic visit) within the first year after enrollment
  - $S(2)$ = all other measured variables between $A(1)$ and $A(2)$, including intermediate outcomes and death
- **A(2)** = Stage 2 "treatment" intervention
  - outreach, SMS and voucher, peer navigator if $L(2) = 1$
  - discontinue, continue if $L(2) = 0$ and $A(1) \in \{$SMS, voucher$\}$
- **Y** = viral suppression at two-years

Outline

What do we know about how the variables relate to each other?

If there were no exclusion restrictions/no assumptions on the functional form...

For observation time $t = 1, \ldots, K$:

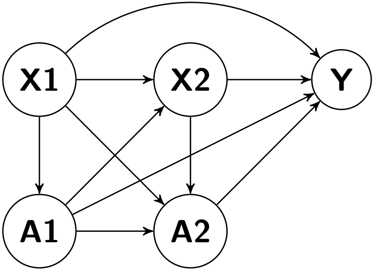
$$
\begin{aligned}
X(t) &= f_{X(t)}(U_{X(t)}, \bar{X}(t-1), \bar{A}(t-1)) \\
A(t) &= f_{A(t)}(U_{A(t)}, \bar{X}(t), \bar{A}(t-1)) \\
Y &= f_Y(U_Y, \bar{X}(K), \bar{A}(K))
\end{aligned}
$$

where exogenous variables are denoted $U = (U_{X(t)}, U_{A(t)}, U_Y)$

What do we know about how the variables relate to each other? 2 time-points

If there were no unmeasured confounders/no exclusion restrictions/assumptions on the functional form...

$$
\begin{aligned}
X(1) &= f_{X(1)}(U_{X(1)}) \\
A(1) &= f_{A(1)}(U_{A(1)}, X(1)) \\
X(2) &= f_{X(2)}(U_{X(2)}, X(1), A(1)) \\
A(2) &= f_{A(2)}(U_{A(2)}, A(1), \bar{X}(2)) \\
Y &= f_Y(U_Y, \bar{X}(2), \bar{A}(2))
\end{aligned}
$$



What do we know about how the variables relate to each other?

For observation time $t = 1, \ldots, K$:

$$\begin{aligned} X(t) &= f_{X(t)}(U_{X(t)}, \bar{X}(t-1), \bar{A}(t-1)) \\ A(t) &= f_{A(t)}(U_{A(t)}, \bar{X}(t), \bar{A}(t-1)) \\ Y &= f_Y(U_Y, \bar{X}(K), \bar{A}(K)) \end{aligned}$$

Is this the correct causal model for SMART data? Should there be any assumptions on dependencies or functional form?

What do we know about how the variables relate to each other?

- Because data were generated from a SMART, treatment assignment at time t only depends on a subset of endogenous variables that occur before $A(t)$ and/or random assignment

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- Because data were generated from a SMART, treatment assignment at time t only depends on a subset of endogenous variables that occur before $A(t)$ and/or random assignment
- Let $\bar{Z}(t) \subseteq (\bar{A}(t-1), \bar{X}(t))$ denote this subset of endogenous tailoring variables used for the SMART's treatment assignment at time t
- Thus, we modify the causal model through $A(t)$. A SMART's causal model is:

$$
\begin{aligned}
X(t) &= f_{X(t)}(U_{X(t)}, \bar{X}(t-1), \bar{A}(t-1)) \\
A(t) &= f_{A(t)}(U_{A(t)}, \bar{Z}(t)) \\
Y &= f_Y(U_Y, \bar{X}(K), \bar{A}(K))
\end{aligned}
$$

for observation time $t = 1, \ldots, K$

ADAPT-R Causal Model

- Causal model for ADAPT-R? How do these variables relate to each other?

ADAPT-R Causal Model

- Causal model for ADAPT-R? How do these variables relate to each other?
- What is $\bar{Z}(2)$?

ADAPT-R Causal Model

$$
\begin{aligned}
X(1) &= f_{X(1)}(U_{X(1)}) \\
A(1) &= f_{A(1)}(U_{A(1)}, Z(1)) \\
X(2) &= f_{X(2)}(U_{X(2)}, X(1), A(1)) \\
A(2) &= f_{A(2)}(U_{A(2)}, \bar{Z}(2)) \\
Y &= f_Y(U_Y, \bar{X}(2), \bar{A}(2))
\end{aligned}
$$

where $\bar{Z}(2) = (A(1), L(2))$, i.e., first stage treatment and whether there was a first-year lapse in care.

ADAPT-R Causal Model

$$
\begin{aligned}
X(1) &= f_{X(1)}(U_{X(1)}) \\
A(1) &= f_{A(1)}(U_{A(1)}, Z(1)) \\
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\end{aligned}
$$

where $\bar{Z}(2) = (A(1), L(2))$, i.e., first stage treatment and whether there was a first-year lapse in care. Specifically...

- $A(1) \sim Multinom(n = 1, k = 3, p_{SMS} = p_{Vouch} = p_{SOC} = \frac{1}{3})$
- $A(2)$ is
  - $\sim Multinom(n = 1, k = 3, p_{SMS+V} = p_{Nav} = p_{SOC} = \frac{1}{3})$ if $L(2) = 1$
  - $\sim Bernoulli(p = \frac{1}{2})$ if $L(2) = 0$ and $A(1) \in \{\text{SMS, Vouch}\}$
  - SOC if $L(2) = 0$ and $A(1) = \text{SOC}$
- $(U_{A(1)}, U_{A(2)})$ are independent of each other and all other Us

Outline

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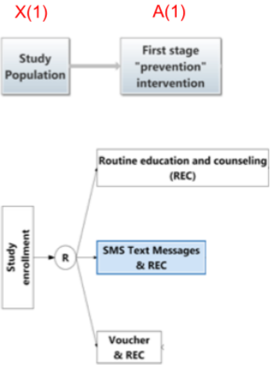
Review: Decision Rules

- A decision rule d_t is a function that takes as input information accrued on a participant up to time t and outputs a treatment decision for $A(t)$
  - $d_t : (\bar{X}(t), \bar{A}(t-1)) \rightarrow \mathcal{A}_t$
  - $\mathcal{D}_t$ is the set of decision rules at time t

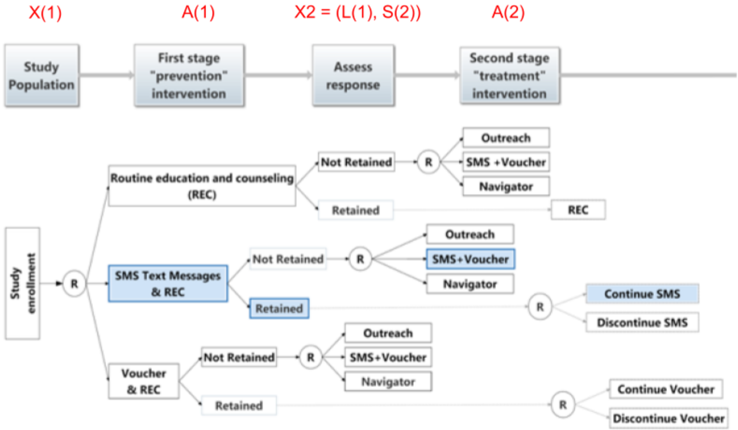
(see PM Lecture 7, slides 9-10)

First Decision Rule - ADAPT-R



First decision rule, $d_1(X(1))$, assigns either SMS, Voucher, or SOC to $A(1)$ based on $X(1)$

Second Decision Rule - ADAPT-R



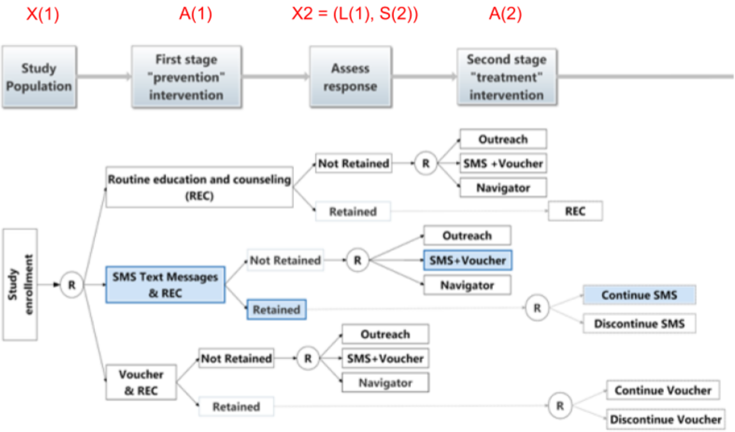
Second decision rule, $d_2(\bar{X}(2), A(1))$, assigns either SMS+Voucher, Nav., SOC, Continue or Discontinue to $A(2)$ based on $X(1)$, $A(1)$, and/or $X(2)$

Review: Dynamic Treatment Regimes

- Let $d = (d_1, d_2, ..., d_K)$ be a dynamic treatment regime (i.e., a sequence of rules)
  - $\mathcal{D}$ is the set of all dynamic treatment regimes

(see PM Lecture 7, slides 9-10)

Dynamic Treatment Regimes - ADAPT-R



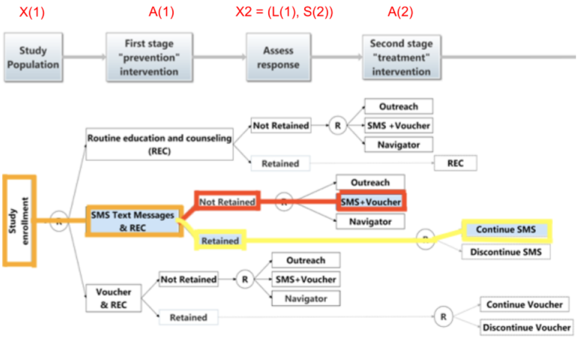
Dynamic regime is $d = (d_1(X(1)), d_2(\bar{X}(2), A(1)))$

Embedded Dynamic Treatment Regimes

A SMART's embedded dynamic treatment regime (AKA embedded regime) is a dynamic treatment regime that will only be a function $\bar{Z}(t)$ (i.e., a SMART's pre-defined tailoring variables)

- i.e., for $t = 1, ..., K$, $d = \big(d_1(Z(1)), ..., d_K(\bar{Z}(K))\big)$
- Let $\mathcal{D}^S \subset \mathcal{D}$ denote the D dynamic treatment regimes embedded within the SMART trial

Embedded Regimes - ADAPT-R



- Embedded regime $d \in \mathcal{D}^S$ is $d = (d_1(Z(1)), d_2(\bar{Z}(2)))$
  - Recall $\bar{Z}(2) = (L(2), A(1))$
  - So $Z(1) = \emptyset$, $Z(2) = (L(2), A(1))$
- Embedded regime example: give everyone SMS; then, give SMS+Voucher if lapse or give Continue SMS if no lapse

ADAPT-R: 15 Embedded Regimes

Embedded Regime #	Stage 1	Stage 2 if Fail	Stage 2 if Succeed
1	SOC	SOC	Continue
2	SMS	SOC	Continue
3	Voucher	SOC	Continue
4	SOC	SMS + Voucher	Continue
5	SMS	SMS + Voucher	Continue
6	Voucher	SMS + Voucher	Continue
7	SOC	Navigator	Continue
8	SMS	Navigator	Continue
9	Voucher	Navigator	Continue
10	SMS	SOC	Discontinue
11	Voucher	SOC	Discontinue
12	SMS	SMS + Voucher	Discontinue
13	Voucher	SMS + Voucher	Discontinue
14	SMS	Navigator	Discontinue
15	Voucher	Navigator	Discontinue

Counterfactual Outcomes

A counterfactual outcome under an embedded regime $d \in \mathcal{D}^S$ is derived under an intervention on the SCM:
For $t = 1, ..., K$:

$$\begin{aligned} X(t) &= f_{X(t)}(U_{X(t)}, \bar{X}(t-1)\bar{A}(t-1)) \\ A(t) &= d_t(\bar{Z}(t)) \\ Y_d &= f_Y(U_Y, \bar{X}(K), \bar{A}(K)) \end{aligned}$$

Y_d is an individual's outcome if, possibly contrary to fact, the individual had been assigned treatment according to the embedded regime d

Causal Question

What are the expected outcomes had all participants received each of the SMART's embedded regimes?

Causal Question/Parameter

What are the expected outcomes had all participants received each of the SMART's embedded regimes?

So, for one $d \in \mathcal{D}^S$:

$$\Psi_d^F(P_{U,X}) = \mathbb{E}_{P_{U,X}}[Y_d]$$

Causal Question/Parameter

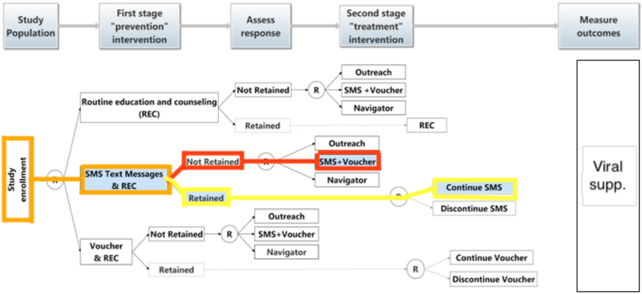
What are the expected outcomes had all participants received each of the SMART's embedded regimes?

So, for one $d \in \mathcal{D}^S$:

$$\Psi^F_d(P_{U,X}) = \mathbb{E}_{P_{U,X}}[Y_d]$$

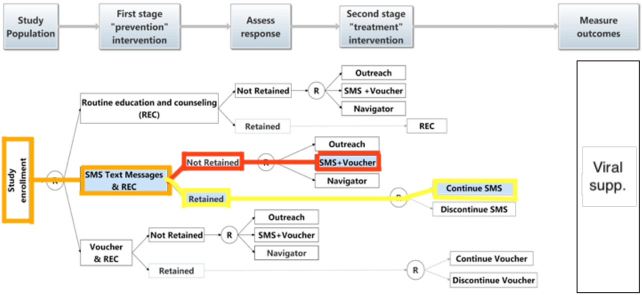
and the vector of the counterfactual values of the D embedded regimes is denoted $\Psi^F(P_{U,X}) = (\Psi^F_{d^{(1)}}(P_{U,X}), ..., \Psi^F_{d^{(D)}}(P_{U,X}))$.

ADAPT-R: Causal Questions/Parameters



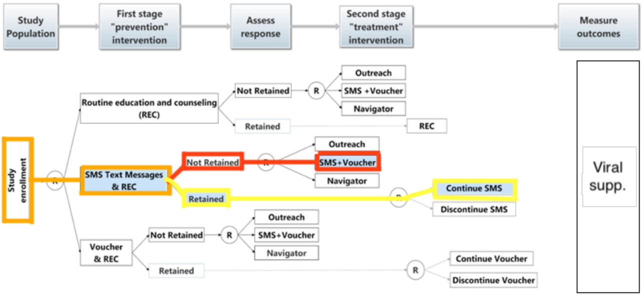
- Prob. 2-yr. viral supp. had all been assigned a specific *embedded regime*?

ADAPT-R: Causal Questions/Parameters



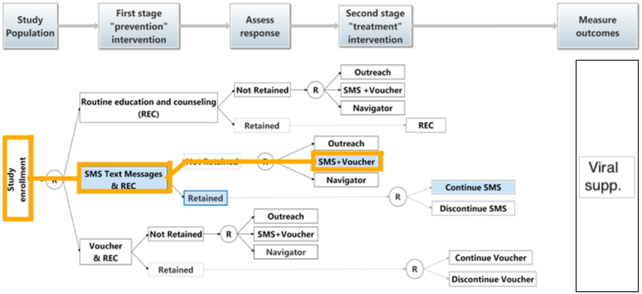
- Prob. 2-yr. viral supp. had all been assigned a specific *embedded regime*?
- More specifically: prob. of 2-yr. viral supp. had everyone been assigned the same prevention intervention, then each person assigned a treatment intervention based on whether or not he/she/they had a lapse in care?

ADAPT-R: Causal Questions/Parameters



- Prob. 2-yr. viral supp. had all been assigned a specific *embedded regime*?
- More specifically: prob. of 2-yr. viral supp. had everyone been assigned the same prevention intervention, then each person assigned a treatment intervention based on whether or not he/she/they had a lapse in care?
  - E.g.: prob. 2-yr. viral supp. had everyone been assigned SMS, then assigned SMS+Voucher if lapse or continue SMS if no lapse
- Causal parameter: $\mathbb{E}_{P_{U,X}}[Y_{A(1)=d_1(Z(1)),A(2)=d_2(\bar{Z}(2))}]$

ADAPT-R: Causal Questions/Parameters



Contrast this with causal question: prob. 2-yr. viral supp. had everyone been assigned SMS, then failed, then assigned SMS+Voucher?

$\mathbb{E}_{P_{U,X}}[Y_{A(1)=a(1),L(2)=1,A(2)=a(2)}]$

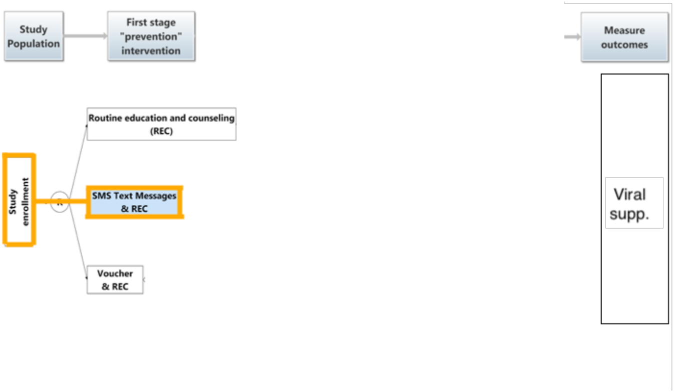
- Here, not evaluating a dynamic regime
- Requires assumptions beyond those satisfied with SMART data because intervening on $L(2)$ (which was not randomized)

Other Causal Parameters/Questions

1. Point treatment static regime: What is the expected outcome had everyone received $A(t) = a(t)$, i.e., $\mathbb{E}[Y_{a(t)}]$?

Other Causal Parameters/Questions

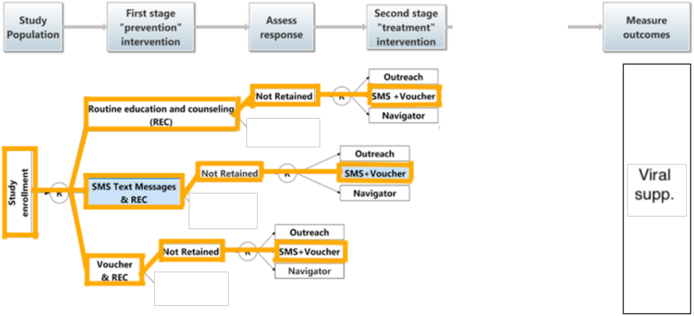
For example...



- Probability of 2-year viral suppression had everyone received the same prevention intervention (e.g., SMS)?
- Causal parameter: $\mathbb{E}[Y_{A(1)=a(1)}]$

Causal Questions

For example...



- Probability of 2-year viral suppression had those who had a lapse in care received the same treatment intervention (e.g., SMS + Voucher)?
- Causal parameter: $\mathbb{E}_{P_{U,X}}[Y_{A(2)=a(2)}|L(2)=1]$

Causal Questions

- In fact, in ADAPT-R, there are 4 simple RCTs pieced together => straightforward answers to causal questions
  - Among all, randomize to prevention intervention
  - Among failures, randomize to intensive intervention
  - Among SMS successes, randomize to discontinue vs. continue
  - Among Voucher successes, randomize to discontinue vs. continue

Causal Questions

1. Point treatment static regime: What is the expected outcome had everyone received $A(t) = a(t)$, i.e., $\mathbb{E}[Y_{a(t)}]$?

    - See, e.g., PM lecture on estimating point-treatment static regimes (Lecture 2)

Causal Questions

1. Point treatment static regime: What is the expected outcome had everyone received $A(t) = a(t)$, i.e., $\mathbb{E}[Y_{a(t)}]$?
    - See, e.g., PM lecture on estimating point-treatment static regimes (Lecture 2)
2. Point treatment optimal dynamic treatment rule: What is the optimal way to assign $A(t)$, i.e., $d_t^*(\bar{X}(t), \bar{A}(t-1)) = \text{argmax}_{d_t \in \mathcal{D}_t} \mathbb{E}[Y_{d_t}]$?
    - See, e.g., PM lecture on single-stage Q-learning and OWL (Lecture 4, 5, & 6)

Causal Questions

1. Point treatment static regime: What is the expected outcome had everyone received $A(t) = a(t)$, i.e., $\mathbb{E}[Y_{a(t)}]$?
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    - See, e.g., PM lecture on single-stage Q-learning and OWL (Lecture 4, 5, & 6)
3. Longitudinal optimal dynamic treatment regime: What is the optimal way to assign $\bar{A}(K)$ in sequence, i.e., $d^* = \text{argmax}_{d \in \mathcal{D}} \mathbb{E}[Y_d]$?
    - See, e.g., PM lecture on multi-stage Q- and A-learning (Lecture 7 & 8)

Outline

Outline

Observed Data & Statistical Model

- Assume the observed data $O_i \equiv (\bar{X}(K)_i, \bar{A}(K)_i, Y_i) \sim P_0 \in \mathcal{M}$, $i = 1, \ldots, n$ were generated by sampling n independent and identically distributed (i.i.d.) times from a data-generating system contained in the causal model
  - Assume ADAPT-R observed data $O_i = (\bar{X}(2)_i, \bar{A}(2)_i, Y_i) \sim P_0 \in \mathcal{M}$, $i = 1, \ldots, 1,809$ were generated by sampling $1,809$ i.i.d. times from a data-generating system contained in the causal model
- P_0 is the observed data distribution, an element of $\mathcal{M}$, the statistical model

Outline

Identification

Two conditions are necessary for identification. What is identification?

For $t = 1, \ldots, K$ and $d \in \mathcal{D}^S$

1. Sequential randomization assumption

$$Y_{d_t} \perp A(t) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))$$

2. Sequential positivity assumption

$$g_0(A(t) = d_t(\bar{Z}(t)) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))) > 0 - a.e.$$

where $g_{A(t),0} = P_0(A(t)|\bar{X}(t), \bar{A}(t-1))$

Identification

Two conditions are necessary for identification; that is, for determining that the causal parameter (a function of the counterfactual distribution, $P_{U,X}$) can be written as statistical parameters (a function of the observed data distribution P_0).

For $t = 1, \ldots, K$ and $d \in \mathcal{D}^S$

1. Sequential randomization assumption

$$Y_{d_t} \perp A(t)|\bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))$$

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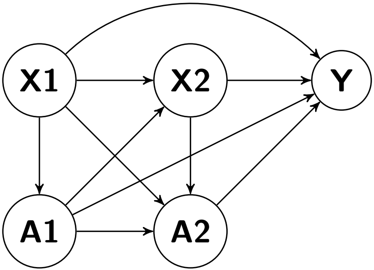
where $g_{A(t),0} = P_0(A(t)|\bar{X}(t), \bar{A}(t-1))$

Why sequential assumptions? A detour...

Suppose this is our SCM (i.e., no unmeasured confounders, no assumptions on dependence or functional form)

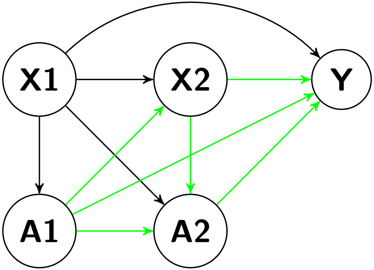
$$
\begin{aligned}
X(1) &= f_{X(1)}(U_{X(1)}) \\
A(1) &= f_{A(1)}(U_{A(1)}, X(1)) \\
X(2) &= f_{X(2)}(U_{X(2)}, X(1), A(1)) \\
A(2) &= f_{A(2)}(U_{A(2)}, A(1), \bar{X}(2)) \\
Y &= f_Y(U_Y, \bar{X}(2), \bar{A}(2))
\end{aligned}
$$



Why sequential assumptions? A detour...

And suppose our target causal parameter is $\mathbb{E}_{P_{U,X}}[Y_{a(1),a(2)}]$

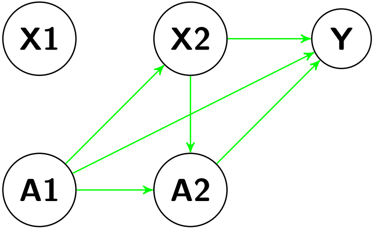
$$\begin{aligned} X(1) &= f_{X(1)}(U_{X(1)}) \\ A(1) &= a(1) \\ X(2) &= f_{X(2)}(U_{X(2)}, X(1), A(1)) \\ A(2) &= a(2) \\ Y &= f_Y(U_Y, \bar{X}(2), \bar{A}(2)) \end{aligned}$$



Why sequential assumptions? A detour...

As in point-treatment case: is conditioning on baseline covariates $X(1)$ enough to identify the effects of both $A(1) = a(1)$, $A(2) = a(2)$ on Y?

$Y_{a(1),a(2)} \perp A(1), A(2) | X(1)$?

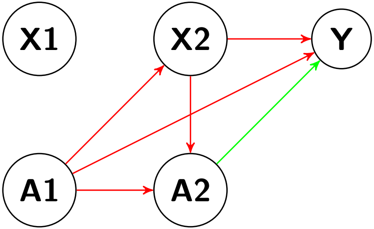


Why sequential assumptions? A detour...

Conditioning on baseline covariates $X(1)$ is **not** enough to identify the effects of both $A(1) = a(1)$, $A(2) = a(2)$ on Y

$Y_{a(1)} \perp A(1)|X(1)$, but
$Y_{a(2)} \not\perp A(2)|X(1)$

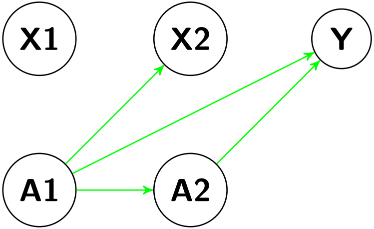
(intuition: $X(2)$ is a confounder for effect of $A(2)$ and Y)



$$\mathbb{E}_{P_{U,X}}[Y_{a(1),a(2)}]$$
$$\neq \sum_{X(1)} \mathbb{E}_0 \left[Y \mid X(1) = x(1), \bar{A}(2) = \bar{a}(2) \right] P_0 \left(X(1) = x(1) \right)$$

Why sequential assumptions? A detour...

Is conditioning on $X(1)$ and $X(2)$ enough to identify the effects of both $A(1) = a(1)$, $A(2) = a(2)$ on Y?



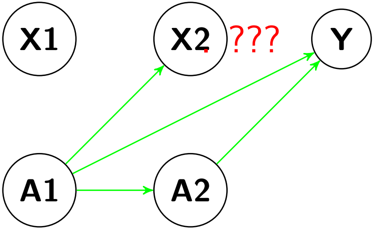
$$Y_{a(1),a(2)} \perp A(1), A(2) | X(1), X(2) \ ?$$

Why sequential assumptions? A detour...

Conditioning on $X(1)$ and $X(2)$ is **not** enough to identify the effects of both $A(1) = a(1)$, $A(2) = a(2)$ on Y

(intuition: losing the effect of $A(1)$ on Y through $X(2)$)

$Y_{a(1)} \not\perp\!\!\!\perp A(1), A(2) | X(1), X(2)$,
and
$Y_{a(2)} \not\perp\!\!\!\perp A(1), A(2) | X(1), X(2)$

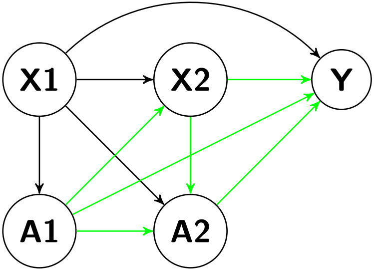


$$\mathbb{E}_{P_{U,X}}[Y_{a(1),a(2)}] \neq \sum_{X(1),X(2)} \mathbb{E}_0 \left[Y \mid \bar{X}(2) = \bar{x}(2), \bar{A}(2) = \bar{a}(2) \right] P_0 \left(\bar{X}(2) = \bar{x}(2) \right)$$

Why sequential assumptions? A detour...

Dilemma of time-dependent confounding:

- Need to standardize with respect to the distribution of both $X(1)$ and $X(2)$ for the effect of both $A1 = a(1)$ and $A2 = a(2)$...
- ...but $X(2)$ are simultaneously *confounders* and *mediators* for that effect



Key Insight

- We don't need to adjust for everything all at once!
- Consider the problem of identifiability *sequentially*
  - For each $A(t)$ in sequence, ask if its effect on Y can be identified by conditioning on some subset of the observed past

Identifiability for the Effects of Multiple Interventions

Sequential Randomization Assumption:

- For 2 timepoints:

$$Y_{a(1),a(2)} \perp A(1)|X(1)$$
$$Y_{a(1),a(2)} \perp A(2)|X(1), A(1), X(2)$$

- For K timepoints:

$$Y_{\bar{a}} \perp A(t)|\bar{X}(t), \bar{A}(t-1) = \bar{a}(t-1), t = 1, \ldots K$$

Identifiability for the Effects of Multiple Interventions

Sequential Randomization Assumption:

- For K timepoints:

$$Y_{\bar{a}} \perp A(t)|\bar{X}(t), \bar{A}(t-1) = \bar{a}(t-1), t = 1, \dots K$$

- When does this hold?
  - If at each time point, A(t) is randomized within strata of (some subset of) covariates and treatment observed up until then
- Then, at each time point the effect of A(t) on future nodes is identified
- (analagous to randomization assumption for a single intervention, which RCTs easily satisfy)

Identifiability for the Effects of Multiple Interventions

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Sound familiar? What is ideal experiment to satisfy the sequential randomization assumption?

Identifiability for the Effects of Multiple Interventions

Sequential Randomization Assumption:

- For K timepoints:

$$Y_{\bar{a}} \perp A(t)|\bar{X}(t), \bar{A}(t-1) = \bar{a}(t-1), t = 1, \ldots K$$

- When does this hold?
  - If at each time point, A(t) is randomized within strata of (some subset of) covariates and treatment observed up until then
- Then, at each time point the effect of A(t) on future nodes is identified
- (analagous to randomization assumption for a single intervention, which RCTs easily satisfy)

The ideal experiment is a SMART!

Identification

Two conditions are necessary for identification:

For $t = 1, \ldots, K$ and $d \in \mathcal{D}^S$

1. Sequential randomization assumption ✓

$$Y_{d_t} \perp A(t) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))$$

2. Sequential positivity assumption

$$g_0(A(t) = d_t(\bar{Z}(t)) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))) > 0 - a.e.$$

where $g_{A(t),0} = P_0(A(t) | \bar{X}(t), \bar{A}(t-1))$

Sequential Positivity Assumption

Analogous to point treatment case, need some positive probability of following regime of interest at each time point, regardless of covariate history

For $t = 1, \ldots, K$ and $d \in \mathcal{D}^S$

$$g_0(A(t) = d_t(\bar{Z}(t)) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))) > 0 - a.e.$$

Does this hold? Why?

Sequential Positivity Assumption

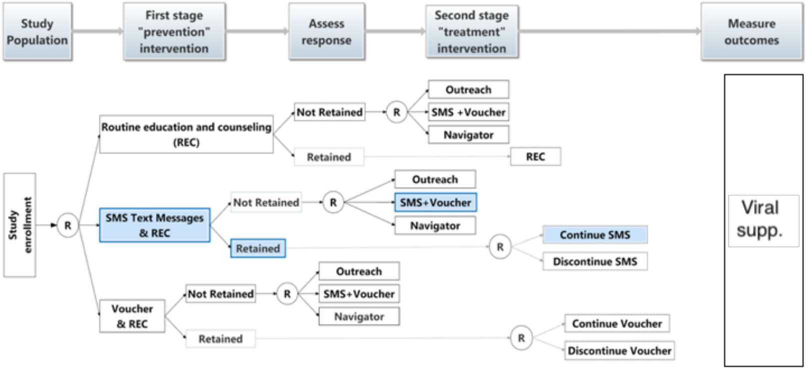
Analogous to point treatment case, need some positive probability of following regime of interest at each time point, regardless of covariate history

For $t = 1, \dots, K$ and $d \in \mathcal{D}^S$

$$g_0(A(t) = d_t(\bar{Z}(t))|\bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))) > 0 - a.e.$$

By design, at each time point, we know the probability $A(t)$ follows the embedded rule $d_t(\bar{Z}(t))$...

Sequential Positivity Assumption



$$g_0(A(1) = d_1(Z(1))|X(1)) = ?$$

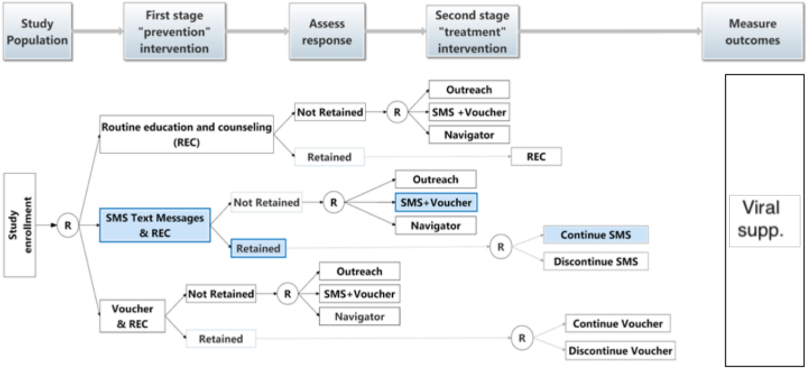
$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = \text{lapse}, S(2), A(1), X(1)) = ?$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = \text{no lapse}, S(2), A(1) = \text{SMS}, X(1)) = ?$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = \text{no lapse}, S(2), A(1) = \text{Voucher}, X(1)) = ?$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = \text{no lapse}, S(2), A(1) = \text{SOC}, X(1)) = ?$$

Sequential Positivity Assumption



$$g_0(A(1) = d_1(Z(1))|X(1)) = 1/3$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = 1, S(2), A(1), X(1)) = 1/3$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = 0, S(2), A(1) = \mathrm{SMS}, X(1)) = 1/2$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = 0, S(2), A(1) = \mathrm{Voucher}, X(1)) = 1/2$$

$$g_0(A(2) = d_2(\bar{Z}(2))|L(2) = 0, S(2), A(1) = \mathrm{SOC}, X(1)) = 1$$

Identification

Two conditions are necessary for identification:

For $t = 1, \ldots, K$ and $d \in \mathcal{D}^S$

1. Sequential randomization assumption ✓

$$Y_{d_t} \perp A(t) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))$$

2. Sequential positivity assumption ✓

$$g_0(A(t) = d_t(\bar{Z}(t)) | \bar{X}(t), \bar{A}(t-1) = \bar{d}_{t-1}(\bar{Z}(t-1))) > 0 - a.e.$$

Outline

Identification Result

Statistical parameter corresponding to causal parameter $\Psi^F_d(P_{U,X})$ for one embedded regime $d = \bar{d}_K(\bar{Z}(K))$ is the g-computation formula:

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

where...

- the summation here generalizes to an integral for continuous $X(t)$
- $\bar{d}_t : (\bar{X}(t), \bar{A}(t-1)) \rightarrow \mathcal{A}_1 \times \ldots \times \mathcal{A}_t$ denotes the regime sequence until time t
  - e.g., $\bar{d}_t(\bar{Z}(t)) = (d_1(Z(1)), d_2(\bar{Z}(2)), ..., d_t(\bar{Z}(t))$ is a SMART's embedded regime until time t

Identification Result

Statistical parameter corresponding to causal parameter $\Psi^F_d(P_{U,X})$ for one of ADAPT's embedded regime:

$$\Psi_d(P_0) = \sum_{x_1,x_2} \mathbb{E}_0 \left[Y|\bar{x}(2), A(1) = d_1(Z(1)), A(2) = d_2(A(1), L(2))\right]$$
$$\times P_0 \left(x(2)|x(1), A(1) = d_1(Z(1))\right)$$
$$\times P_0 \left(x(1)\right)$$

The vector of all embedded regime values is identified as $\Psi(P_0) = (\Psi_{d^{(1)}}(P_0), ..., \Psi_{d^{(D)}}(P_0))$; in ADAPT-R, $D = 15$.

Outline

Outline

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Outline

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