

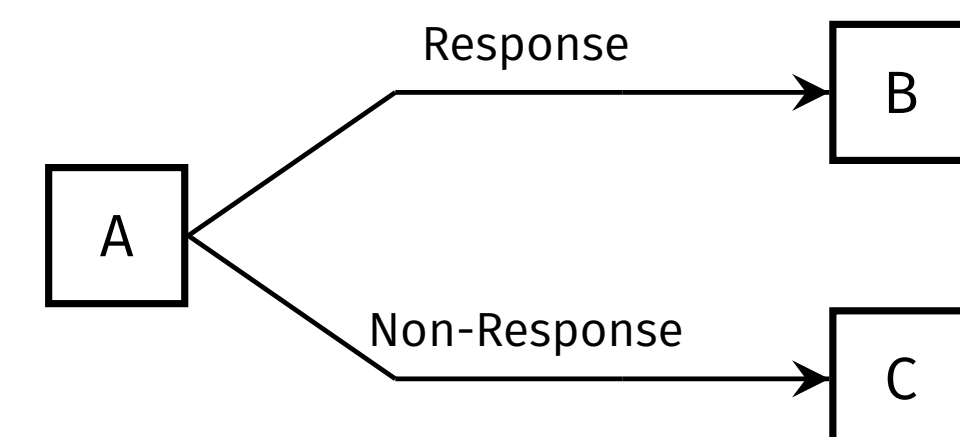
Sample size considerations for comparing dynamic treatment regimens in a sequential multiple-assignment randomized trial with a continuous longitudinal outcome

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Dynamic Treatment Regimens

A **dynamic treatment regimen (DTR)** is a sequence of pre-specified decision rules which guides the delivery of an individualized sequence of treatments. This sequence is tailored based on ongoing information about the individual's progress in treatment.



Sequential Multiple-Assignment Randomized Trials

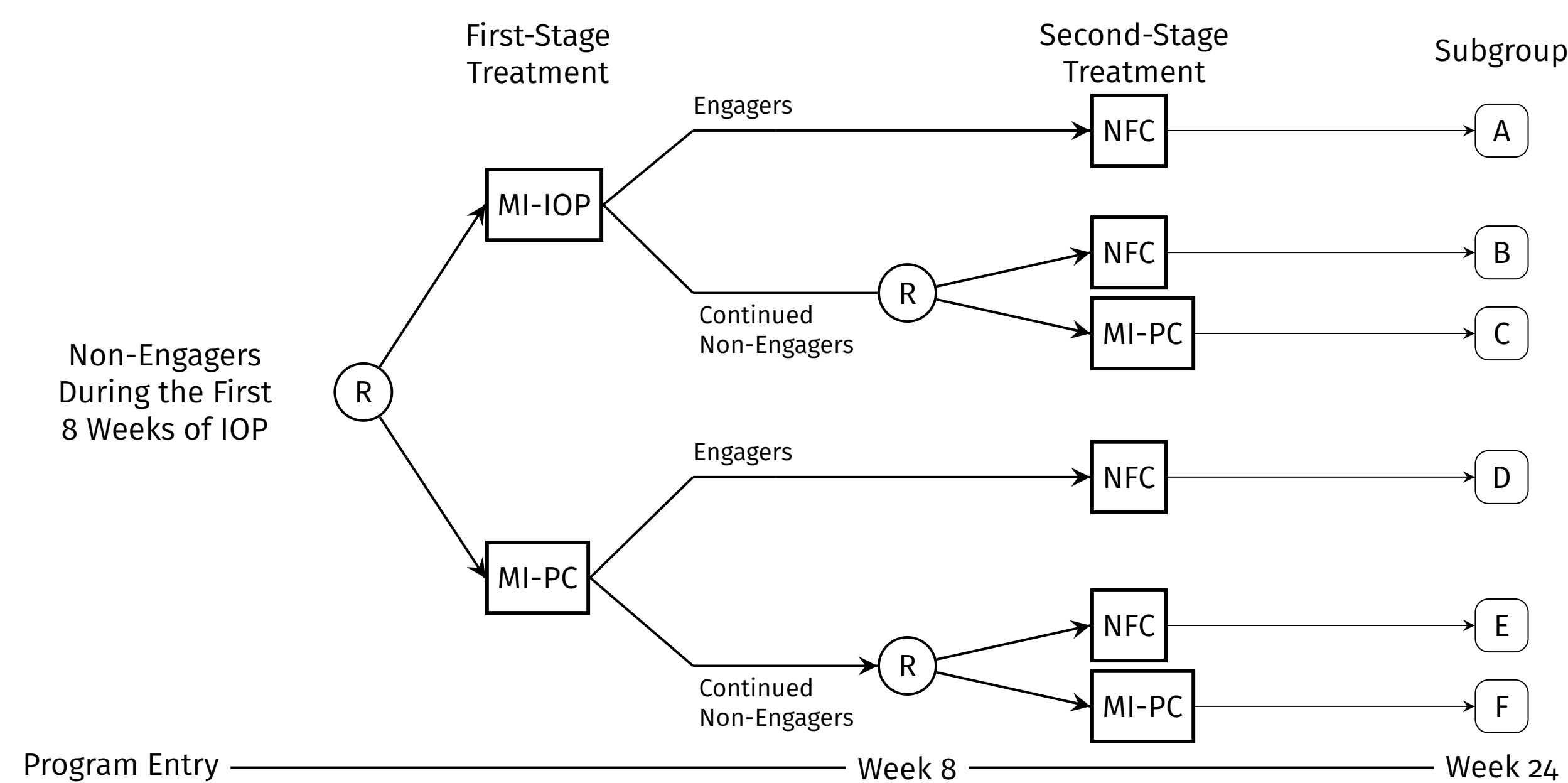
A **sequential multiple-assignment randomized trial (SMART)** is an experimental design which can provide data that informs the construction of an effective DTR (Murphy, 2005). Some or all participants are randomized more than once. Each randomization corresponds to a critical question regarding the development of a DTR.

We consider two-stage SMARTs in which the primary outcome is continuous and repeatedly measured in participants over the course of the study.

The ENGAGE Trial

The ENGAGE study (J. McKay, PI; N = 500) is a SMART aimed at developing a DTR to increase motivation to engage in treatment among alcohol- and cocaine-dependent patients.

Figure 1: Diagram of the ENGAGE SMART. Circled R indicates randomization, boxes indicate treatments. MI-IOP refers to two phone-based sessions encouraging participation in an intensive outpatient program; MI-PC, two phone-based sessions offering patients a choice of treatment modalities; NFC is no further contact.



- The outcome of interest is **treatment readiness**, a measure of a patient's willingness and ability to commit to active participation in a substance abuse treatment program.
- Treatment readiness was assessed using an 8-item questionnaire scored from 0 to 40 and coded such that higher scores are better. We consider measurements taken at baseline and at weeks 8 and 24.
- There are 4 **embedded DTRs**, indexed by recommended first-stage treatment a_1 and recommended second-stage treatment for continued non-engagers, a_2 .

(a_1, a_2)	Stage 1 Treatment	Stage 2 Treatment		Subgroups
		Engagers	Ctd. Non-Engagers	
(1, 1)	MI-IOP	NFC	MI-PC	A, C
(1, -1)	MI-IOP	NFC	NFC	A, B
(-1, 1)	MI-PC	NFC	MI-PC	D, F
(-1, -1)	MI-PC	NFC	NFC	D, E

Marginal Mean Model

We are interested in $E[Y_t^{(a_1, a_2)} | X]$, the marginal mean of $Y^{(a_1, a_2)}$ at time t under DTR (a_1, a_2) conditional on X . This is the mean outcome at time t had all individuals with characteristics X been offered DTR (a_1, a_2) .

- We impose a modeling assumption:

$$E[Y_t^{(a_1, a_2)} | X] = \mu_t^{(a_1, a_2)}(X; \theta),$$

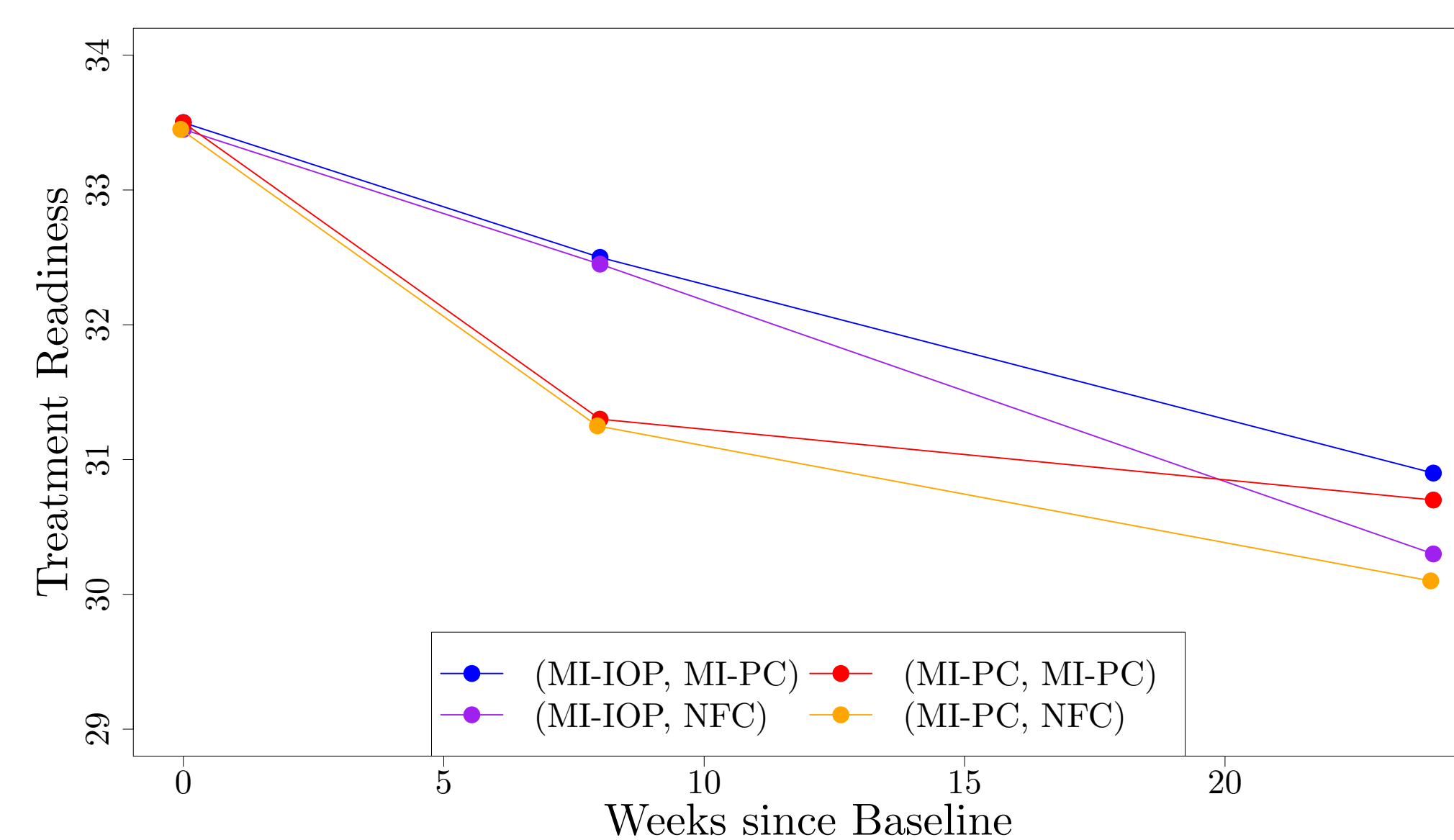
where $\mu_t^{(a_1, a_2)}(X; \theta)$ is a **marginal structural mean model** with unknown parameters $\theta = (\eta, \gamma)$.

- $\mu_t^{(a_1, a_2)}(X; \theta)$ should account for the design of the SMART.
- An example model for ENGAGE is

$$\begin{aligned} \mu_t^{(a_1, a_2)}(X; \theta) = & \eta^\top X + \gamma_0 + \mathbb{1}_{\{t \leq 8\}}(\gamma_1 t + \gamma_2 a_1 t) \\ & + \mathbb{1}_{\{t > 8\}}(8\gamma_1 + 8\gamma_2 a_1 + \gamma_3(t-8) + \gamma_4(t-8)a_1 \\ & + \gamma_5(t-8)a_2 + \gamma_6(t-8)a_1 a_2), \end{aligned}$$

where $\mathbb{1}_{\{E\}}$ is the indicator function for the event E .

Figure 2: Plot of treatment readiness vs. time using data from ENGAGE.



Estimation of Model Parameters

The estimate $\hat{\theta}$ of θ is the solution to the following the estimating equations:

Estimating Equations

$$0 = \frac{1}{n} \sum_{i=1}^n \sum_{(a_1, a_2)} \left[W^{(a_1, a_2)}(A_{1,i}, R_i, A_{2,i}) \cdot D^{(a_1, a_2)}(X_i)^\top V^{(a_1, a_2)}(X_i)^{-1} (Y_i - \mu^{(a_1, a_2)}(X_i; \theta)) \right]$$

where

- (a_1, a_2) specifies an embedded DTR,
- $W^{(a_1, a_2)}(A_{1,i}, R_i, A_{2,i}) = 2 \cdot \mathbb{1}\{A_{1,i} = a_1\} (R_i + 2(1-R_i)\mathbb{1}\{A_{2,i} = a_2\})$
- $D^{(a_1, a_2)}(X_i) = \frac{\partial}{\partial \theta} \mu^{(a_1, a_2)}(X_i; \theta)$
- $V^{(a_1, a_2)}(X_i)$ is a working model for $\text{Var}(Y^{(a_1, a_2)} - \mu^{(a_1, a_2)}(X_i; \theta) | X_i)$

Assuming that $\mu^{(a_1, a_2)}(X_i; \theta)$ is correctly specified, $\hat{\theta}$ is consistent for the true parameter value, regardless of the choice of $V^{(a_1, a_2)}(X_i)$ (Lu et al., 2016). Under usual regularity conditions for M -estimators and given data from a SMART, $\sqrt{n}(\hat{\theta} - \theta)$ has an asymptotic multivariate normal distribution: $\sqrt{n}(\hat{\theta} - \theta) \Rightarrow \mathcal{N}(0, B^{-1}MB^{-1})$, where

- $B := E \left[\sum_{(a_1, a_2)} W^{(a_1, a_2)}(A_{1,i}, R_i, A_{2,i}) D^{(a_1, a_2)}(X_i)^\top V^{(a_1, a_2)}(X_i)^{-1} D^{(a_1, a_2)}(X_i) \right]$
- $M := E \left[\left(\sum_{(a_1, a_2)} W^{(a_1, a_2)}(A_{1,i}, R_i, A_{2,i}) D^{(a_1, a_2)}(X_i)^\top V^{(a_1, a_2)}(X_i)^{-1} (Y_i - \mu^{(a_1, a_2)}(X_i; \theta)) \right)^{\otimes 2} \right]$

Sample Size

We developed a sample size formula for an ENGAGE-style SMART with a continuous longitudinal outcome in which the primary aim is to compare two embedded DTRs which recommend different first-stage treatments on the end-of-study measurement. We ignore baseline covariates and consider three timepoints, $t = 0, 1, 2$.

To compare DTRs $(1, 1)$ and $(-1, -1)$, we size the trial based on a Wald test of

$$H_0: c^\top \theta = 0 \quad \text{vs.} \quad H_1: c^\top \theta = \Delta,$$

where c is a contrast vector such that $c^\top \theta = E[Y_2^{(1,1)} - Y_2^{(-1,-1)}]$. The test statistic is

$$Z = \frac{\sqrt{n} c^\top \hat{\theta}}{\sigma_c}.$$

We make three working assumptions to simplify the form of $\sigma_c = \sqrt{c^\top B^{-1} M B^{-1} c}$:

- The variance in the outcome among non-responders after the second randomization is not too much larger than the corresponding variances in responders,
- $\text{Cov}(Y_t^{(a_1, a_2)}, Y_2^{(a_1, a_2)} | R^{(a_1)} = 1) \leq \text{Cov}(Y_t^{(a_1, a_2)}, Y_2^{(a_1, a_2)} | R^{(a_1)} = 0)$ for $t = 0, 1$,
- The marginal variance of $Y^{(a_1, a_2)}$ is constant across time and DTR, and has an exchangeable correlation structure with correlation ρ , i.e., $\text{Var}(Y^{(a_1, a_2)}) = \sigma^2 \text{Exch}_3(\rho)$.

Suppose we want to detect a **standardized effect size** $\delta = \Delta/\sigma$. Define r_{a_1} to be the probability of response to first-stage treatment a_1 .

Sample Size Formula for an ENGAGE-Type SMART

$$n \geq \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \cdot (1 - \rho^2) \cdot \left(2 - \frac{1}{2}(r_1 + r_{-1})\right)$$

The sample size formula is the product of three components: (1) the formula for the minimum sample size for the comparison of two means in a standard two-arm trial, (2) a deflation factor of $1 - \rho^2$ that accounts for the use of a longitudinal outcome, and (3) a SMART-specific "design effect", an inflation factor that accounts for the SMART design.

Table 1: Example sample sizes for comparing the end-of-study outcomes of two embedded DTRs in an ENGAGE-type SMART which start with different treatments. $r_1 = r_{-1} = 0.4$, $\alpha = 0.05$ (two-sided), and $\beta = 0.2$.

Std. Effect Size	Within-Person Correlation		
	$\rho = 0$	$\rho = 0.3$	$\rho = 0.6$
$\delta = 0.3$	559	508	358
$\delta = 0.5$	201	183	129
$\delta = 0.8$	79	72	51

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