Sample Size Considerations for the Analysis of Continuous Repeated-Measures Outcomes in Sequential Multiple-Assignment Randomized Trials

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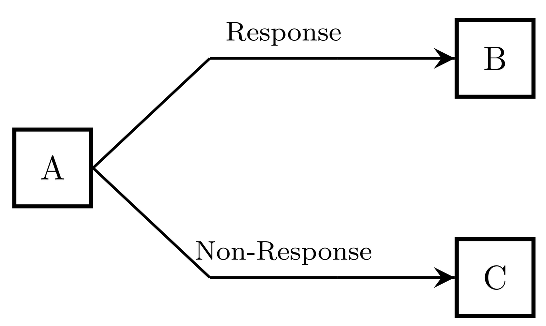
Dynamic Treatment Regimes

A **dynamic treatment regime (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.



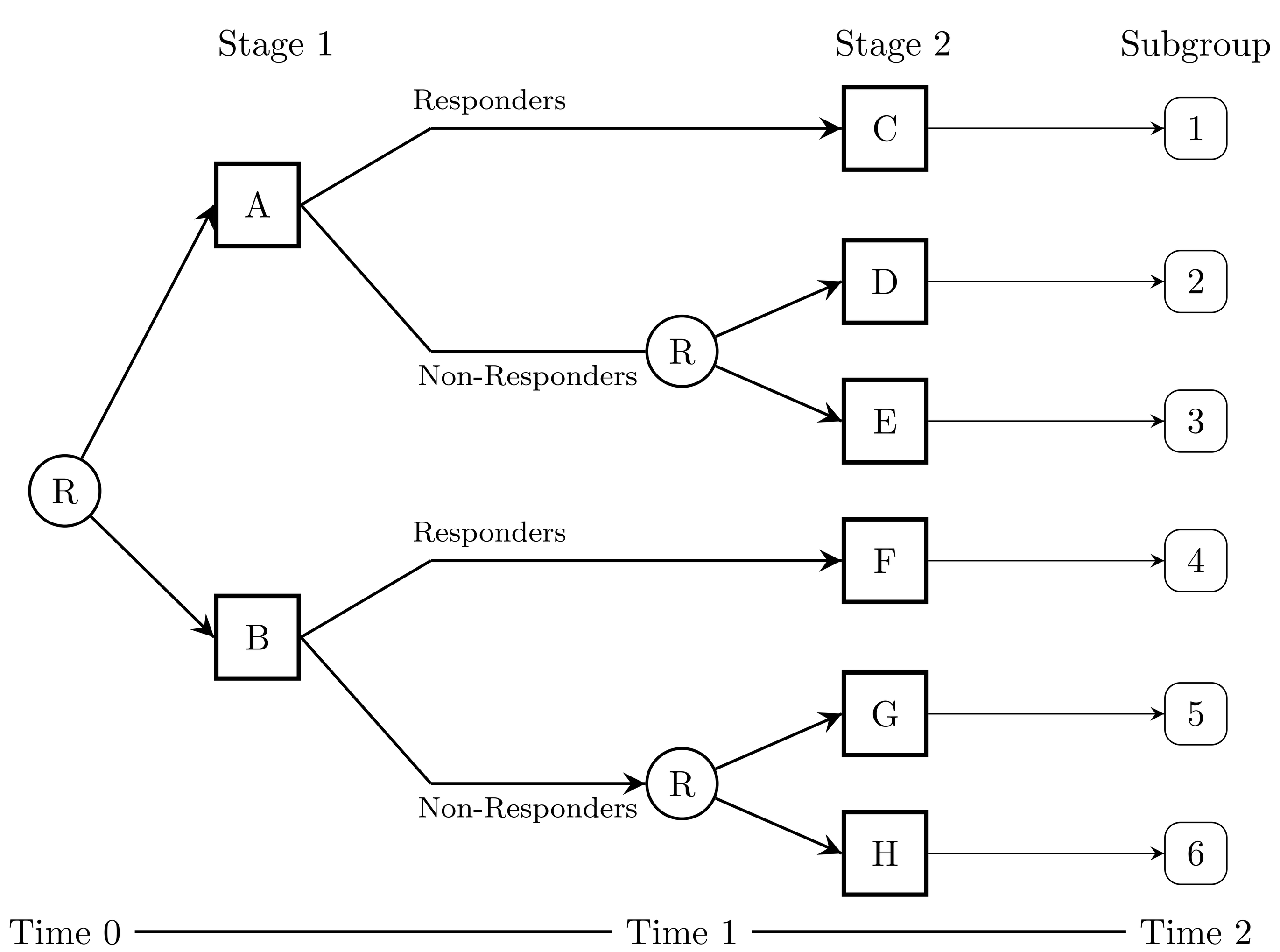
Sequential Multiple-Assignment Randomized Trials

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.

The ENGAGE Trial

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

Figure 1: Diagram of the ENGAGE SMART. Circled R indicates randomization, boxes indicate treatments. MI-IOP corresponds to two motivational interviews encouraging participation in the IOP; MI-PC, two motivational interviews 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 first-stage treatment and second-stage treatment for continued non-engagers.

Table 1: Embedded DTRs in ENGAGE

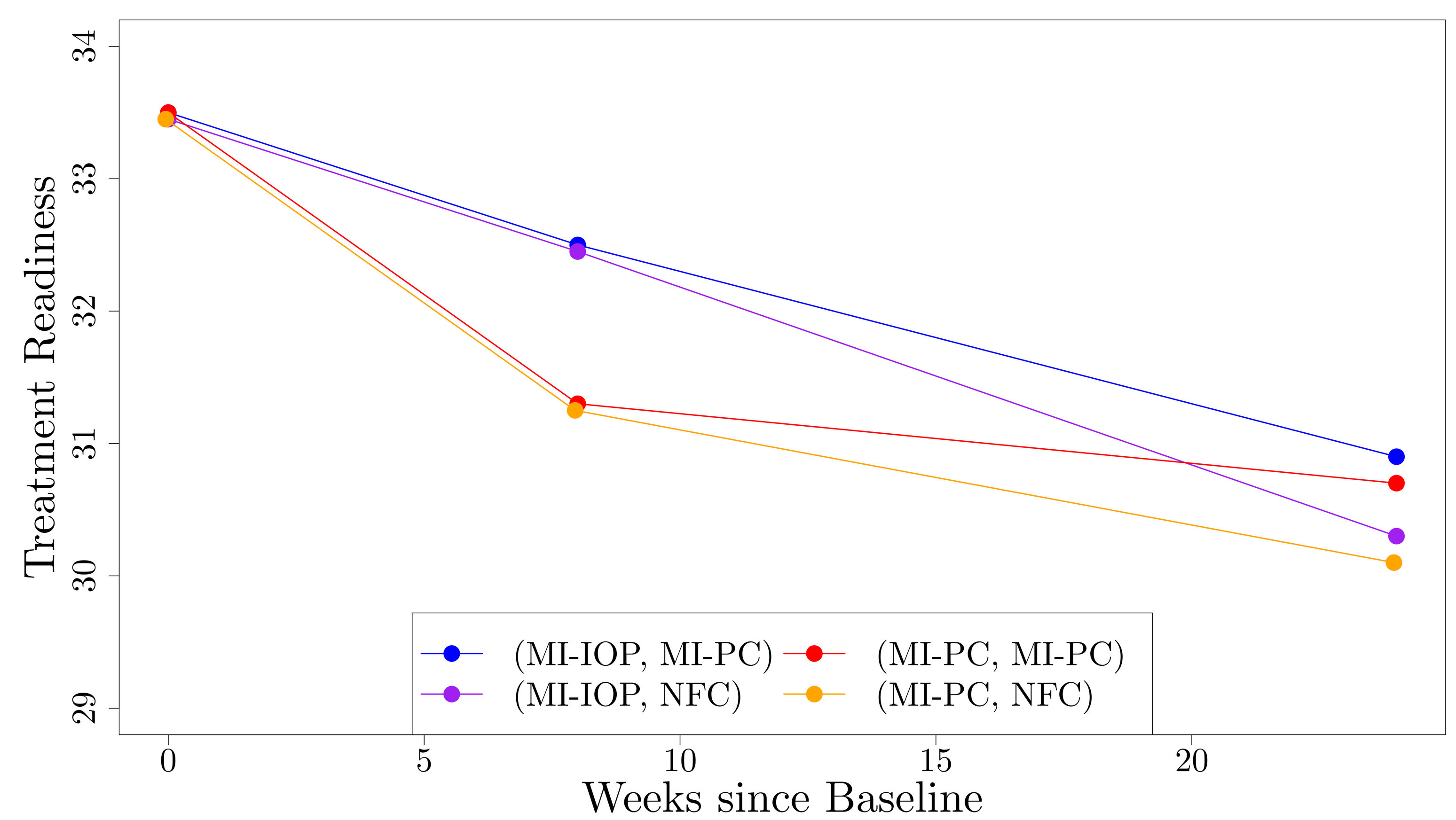
		Stage 2 Treatment		
(a_1, a_2)	Stage 1 Treatment	Engagers	Ctd. Non-Engagers	Subgroups

Marginal Mean Model

We are interested in $E\left[Y_t^{(a_1,a_2)} \mid \boldsymbol{X}\right]$, the marginal mean of $\boldsymbol{Y}^{(a_1,a_2)}$ at time t under DTR (a_1, a_2) conditional on baseline covariates $\boldsymbol{X}$.

- We impose a modeling assumption:
$$E[Y_t^{(a_1,a_2)} \mid \boldsymbol{X}] = \mu_t^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta}),$$
where $\mu_t^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta})$ is a **marginal structural mean model** with unknown parameters $\boldsymbol{\theta} = (\boldsymbol{\eta}, \boldsymbol{\gamma})$.
- $\mu_t^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta})$ should account for the design of the SMART.
- An example model for ENGAGE is
$$\begin{aligned}\mu_t^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta}) &= \boldsymbol{\eta}^\top \boldsymbol{X} + \gamma_0 \\ &+ \mathbb{1}_{\{t\le 8\}}\left(\gamma_1 t + \gamma_2 a_1 t\right) + \mathbb{1}_{\{t>8\}}\left(8\gamma_1 + 8\gamma_2 a_1 + \gamma_3(t-8)\right. \\ &\left.+\gamma_4(t-8)a_1 + \gamma_5(t-8)a_2 + \gamma_6(t-8)a_1a_2\right), \quad t = 0, 8, 24\end{aligned}$$

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



Estimation of Model Parameters

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

Estimating Equations

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

where

- (a_1, a_2) specifies an embedded DTR,
- $W^{(a_1,a_2)}\left(A_{1,i}, R_i, A_{2,i}\right) = 2 \cdot \mathbb{1}\{A_{1,i} = a_1\}\left(R_i + 2(1-R_i)\mathbb{1}\{A_{2,i} = a_2\}\right)$
- $\boldsymbol{D}^{(a_1,a_2)}(\boldsymbol{X}_i) = \frac{\partial}{\partial\boldsymbol{\theta}}\boldsymbol{\mu}^{(a_1,a_2)}(\boldsymbol{X}_i;\boldsymbol{\theta})$
- $\boldsymbol{V}^{(a_1,a_2)}(\boldsymbol{X}_i)$ is a working model for $\mathrm{Var}\left(\boldsymbol{Y}^{(a_1,a_2)} - \boldsymbol{\mu}^{(a_1,a_2)}(\boldsymbol{X}_i;\boldsymbol{\beta}) \mid \boldsymbol{X}_i\right)$

Assuming that $\boldsymbol{\mu}^{(a_1,a_2)}(\boldsymbol{X}_i;\boldsymbol{\theta})$ is correctly specified, $\hat{\boldsymbol{\theta}}$ is consistent for the true parameter value, regardless of the choice of $\boldsymbol{V}^{(a_1,a_2)}(\boldsymbol{X}_i)$ (Lu et al., 2016).

Sample Size

We developed a sample size formula for a SMART with a continuous repeated-measures outcome in which the primary aim is to compare two embedded DTRs (with different first-stage treatments) on the end-of-study measurement.

To compare DTRs $(1, 1)$ and $(-1, 1)$, we size the trial based on a Wald test:
$$H_0: 16\gamma_2 + 32\gamma_4 + 32\gamma_6 = 0 \quad \text{vs.} \quad H_1: 16\gamma_2 + 32\gamma_4 + 32\gamma_6 \neq 0.$$

We assume:

1. The probability of response is the same for both first-stage treatments: $P(R = 1 \mid A_1 = 1) = P(R = 1 \mid A_1 = -1) = r$
2. The variance of $(\boldsymbol{Y}^{(a_1,a_2)} - \boldsymbol{\mu}^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta}))$ is unconditional on response:
$$\mathrm{Var}\left(\boldsymbol{Y}^{(a_1,a_2)} - \boldsymbol{\mu}^{(a_1,a_2)} \mid R = 1\right) = \mathrm{Var}\left(\boldsymbol{Y}^{(a_1,a_2)} - \boldsymbol{\mu}^{(a_1,a_2)} \mid R = 0\right)$$
3. The true covariance structure of $(\boldsymbol{Y}^{(a_1,a_2)} - \boldsymbol{\mu}^{(a_1,a_2)}(\boldsymbol{X};\boldsymbol{\theta}))$ is $\sigma^2\boldsymbol{R}(\rho)$, where $\boldsymbol{R}(\rho)$ is an exchangeable correlation matrix with correlation ρ.

Suppose we want to detect a standardized effect size $\boldsymbol{\delta}$. The sample size for the SMART is

Sample Size Formula

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

Below is a selection of minimum-required sample sizes for comparing two embedded DTRs in an ENGAGE-type SMART which start with different treatments. Sample sizes are based on a comparison of an end-of-study outcome, and vary with minimum-detectable standardized effect size and within-person correlation among the repeated measures.

Table 2: Example sample sizes for comparison of two embedded DTRs. $r = 0.4$, $\alpha = 0.05$ (two-sided), and $\beta = 0.2$.

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

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