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

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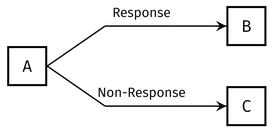
Dynamic Treatment Regimens

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.



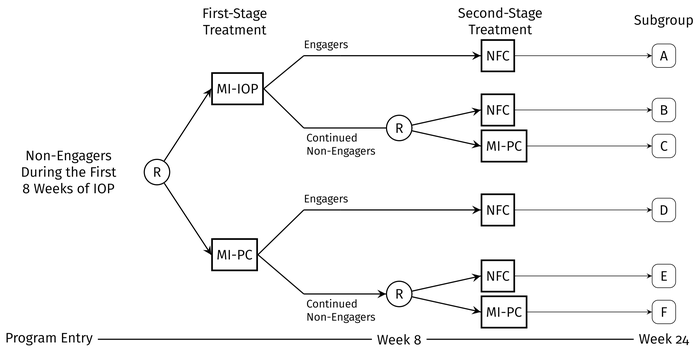
Sequential Multiple-Assignment Randomized Trials

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.

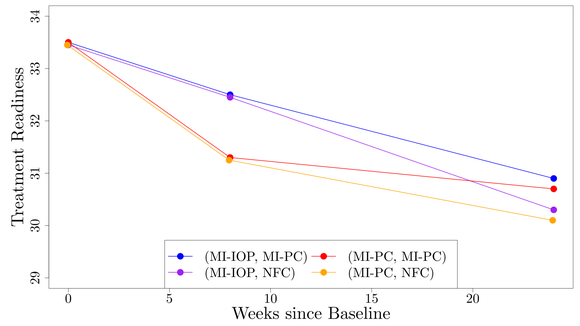
		Stage 2 Treatment		
(a_1, a_2)	Stage 1 Treatment	Engagers	Ctd. Non-Engagers	Subgroups
$(1,1)$	MI-IOP	NFC	MI-PC	A, C
$(1,-1)$	MI-IOP	NFC	NFC	A, B
$(-1,1)$	MI-PC	NFC	MI-PC	D, F
$(-1,-1)$	MI-PC	NFC	NFC	D, E

Marginal Mean Model

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

- 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
$$\begin{aligned}\mu_t^{(a_1,a_2)}(\boldsymbol{X}; \boldsymbol{\theta}) = \boldsymbol{\eta}^\top \boldsymbol{X} &+ \gamma_0 + \mathbb{1}_{\{t \le 8\}}\left(\gamma_1 t + \gamma_2 a_1 t\right) \\ &+ \mathbb{1}_{\{t>8\}}\left(8\gamma_1 + 8\gamma_2 a_1 + \gamma_3(t-8) + \gamma_4(t-8)a_1 \right. \\ &\left. + \gamma_5(t-8)a_2 + \gamma_6(t-8)a_1 a_2\right),\end{aligned}$$
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 $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$ is the solution to the following the estimating equations:

Estimating Equations

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

where

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

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 $\boldsymbol{V}^{(a_1,a_2)}\left(\boldsymbol{X}_i\right)$ (Lu et al., 2016). Under usual regularity conditions for M-estimators and given data from a SMART, $\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})$ has an asymptotic multivariate normal distribution: $\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}) \Rightarrow \mathcal{N}(\mathbf{0}, \boldsymbol{B}^{-1}\boldsymbol{M}\boldsymbol{B}^{-1})$, where

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

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

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

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

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

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

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

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

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

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 $\beta = 0.2$.

	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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