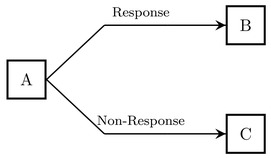
Sample Size Considerations for the Analysis of Continuous Repeated-Measures Outcomes in Sequential Multiple-Assignment Randomized Trials

Nicholas J. Seewald [1] Inbal Nahum-Shani [2] James R. McKay [3] Daniel Almirall [2]

[1]Department of Statistics, University of Michigan [2]Survey Research Center, Institute for Social Research, University of Michigan [3]Department of Psychiatry, University of Pennsylvania

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.



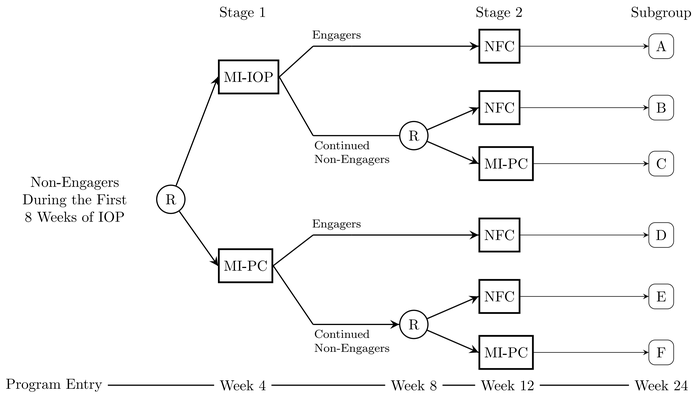
Sequential Multiple-Assignment Randomized Trials

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
$(1, 1)$	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 $E\left[Y_t^{(a_1,a_2)} \mid \boldsymbol{X}\right]$, the marginal mean of $\boldsymbol{Y}^{(a_1,a_2)}$ at time t under DTR (a_1, a_2) conditional on baseline covariates $\boldsymbol{X}$.

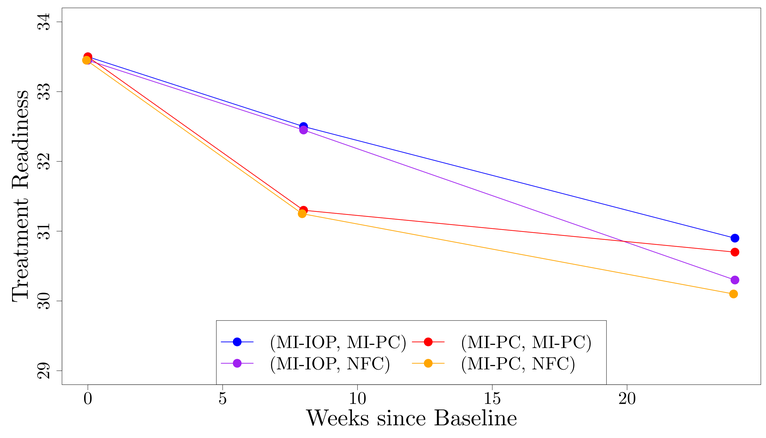
- We impose a modeling assumption:

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

  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

$$\begin{aligned}\mu_t^{(a_1,a_2)}(\boldsymbol{X}; \boldsymbol{\theta}) = \boldsymbol{\eta}^\top \boldsymbol{X} + \gamma_0 \\ + \mathbb{1}_{\{t \le 8\}}\left(\gamma_1 t + \gamma_2 a_1 t\right) + \mathbb{1}_{\{t > 8\}}\left(8\gamma_1 + 8\gamma_2 a_1 + \gamma_3(t-8)\right. \\ \left. + \gamma_4(t-8)a_1 + \gamma_5(t-8)a_2 + \gamma_6(t-8)a_1 a_2\right), \quad t = 0, 8, 24\end{aligned}$$

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

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

where

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

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

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

Acknowledgements

We wish to thank Kelley M. Kidwell, Ph.D., and Tianshuang Wu, Ph.D., for input and assistance in work leading to this poster.
This work was supported by the following awards from the National Institutes of Health: R01DA039901, P50DA039838, R01HD073975, R03MH097954, P01AA016821, RC1AA019092, U54EB020404.

References

Lu, X., I. Nahum-Shani, C. Kasari, K. G. Lynch, D. W. Oslin, W. E. Pelham, G. Fabiano, and D. Almirall (2016). Comparing dynamic treatment regimes using repeated-measures outcomes: Modeling considerations in SMART studies. *Stat. Med. 35*(10), 1595–1615.

Murphy, S. A. (2005). An experimental design for the development of adaptive treatment strategies. *Stat. Med. 24*(10), 1455–1481.

Contact Information

- Email: `nseewald@umich.edu`
- Web: `http://nickseewald.com`

LSA STATISTICS UNIVERSITY OF MICHIGAN