Sample Size Considerations for Comparing Dynamic Treatment Regimens in a Sequential Multiple-Assignment Randomized Trial with a Continuous Longitudinal Outcome

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Nicholas J. Seewald
Kelley M. Kidwell, James R. McKay, Inbal Nahum-Shani, Daniel Almirall

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Department of Statistics
University of Michigan

Motivating Example: The ENGAGE Study (McKay, et al., 2015)

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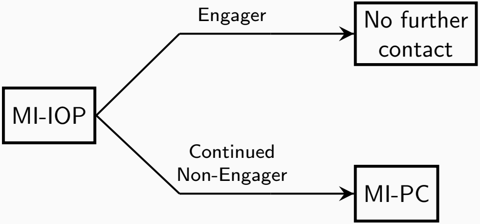
- For these individuals, should we attempt to re-engage them in their original treatment, or offer them a choice of treatment modality?
- What do we do if that doesn't work?
- This is a question about a *sequence* of treatments.

Dynamic Treatment Regimens

Dynamic treatment regimens operationalize clinical decision-making by recommending particular treatments to certain subsets of patients at specific times. (Chakraborty and Moodie, 2013)



- **MI-IOP**: 2 motivational interviews to re-engage patient in intensive outpatient program
- **MI-PC**: 2 motivational interviews to engage patient in treatment of their choice.

Sequential, Multiple-Assignment Randomized Trials

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The key feature of a SMART is that some (or all) participants are randomized *more than once*.

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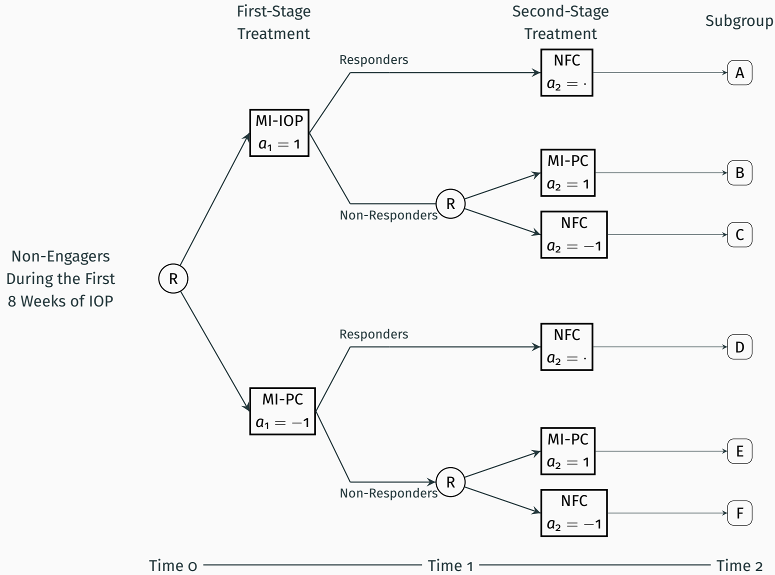
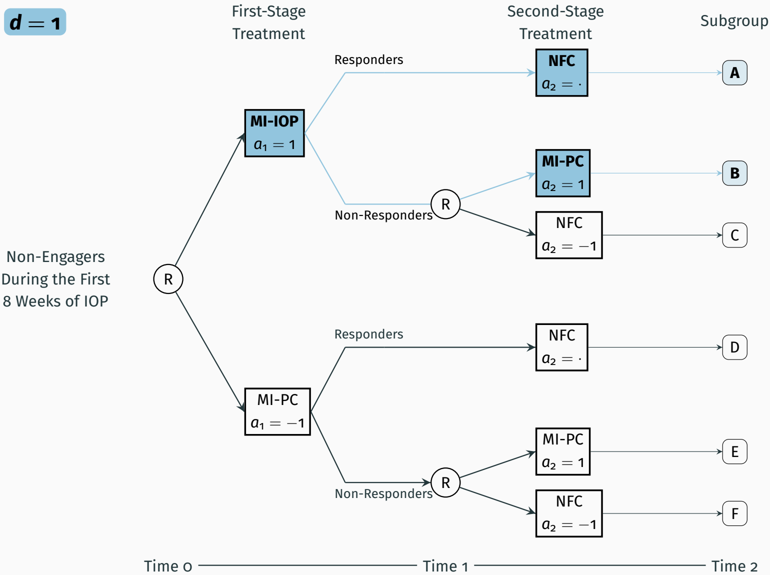


Four Embedded DTRs



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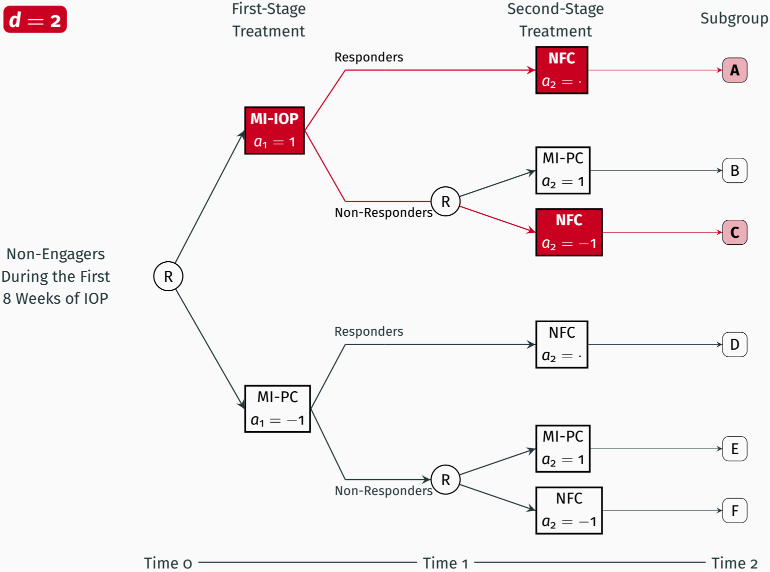

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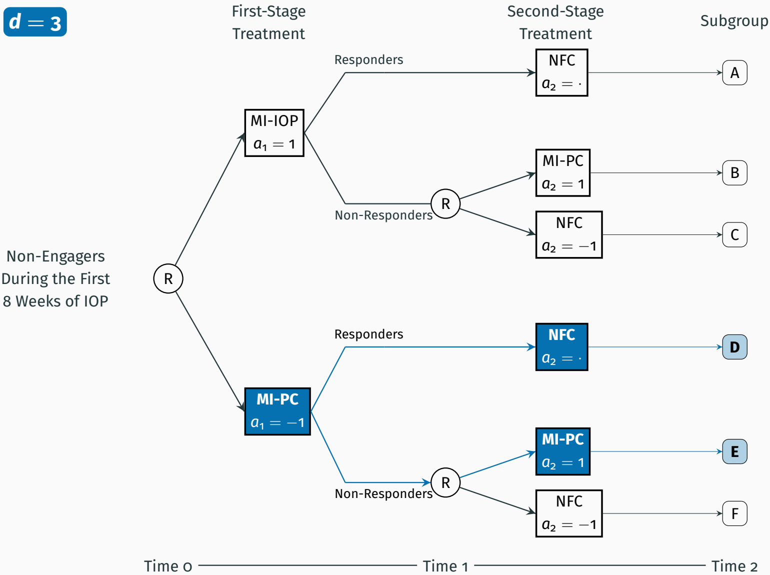

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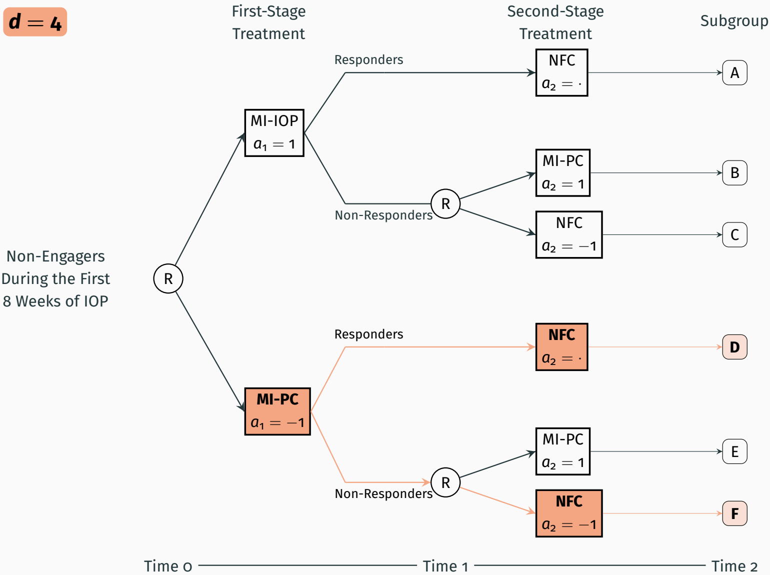
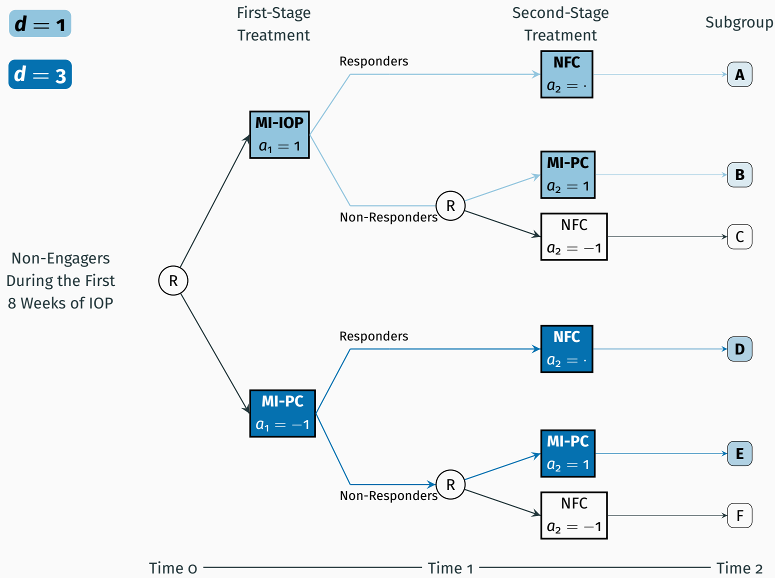


A common primary aim in a SMART

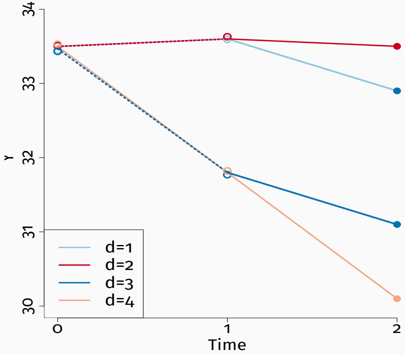
is the comparison of two embedded DTRs using a continuous outcome collected at the end of the study.

Primary Aim



$d = 1$
$d = 3$
First-Stage Treatment
Second-Stage Treatment
Subgroup
Non-Engagers During the First 8 Weeks of IOP
R
MI-IOP $a_1 = 1$
MI-PC $a_1 = -1$
Responders
Non-Responders
R
NFC $a_2 = \cdot$
MI-PC $a_2 = 1$
NFC $a_2 = -1$
A
B
C
Responders
Non-Responders
R
NFC $a_2 = \cdot$
MI-PC $a_2 = 1$
NFC $a_2 = -1$
D
E
F
Time 0
Time 1
Time 2

A Model for a Continuous Longitudinal Outcome in ENGAGE (Lu, et al., 2016)



$$
\begin{aligned}
E_{(d)}\left[Y_t \mid \boldsymbol{X}\right] &:= \mu^{(d)}(\boldsymbol{X}_i; \eta, \gamma) \\
&= \eta^\top \boldsymbol{X}_i + \gamma_0 \\
&\quad + \mathbb{1}_{\{t \le 1\}}\left\{\gamma_1 t + \gamma_2 a_1 t\right\} \\
&\quad + \mathbb{1}_{\{t > 1\}}\left\{\gamma_1 + \gamma_2 a_1 \right. \\
&\qquad + \gamma_3(t-1) + \gamma_4(t-1)a_1 \\
&\qquad + \gamma_5(t-1)a_2 \\
&\qquad \left. + \gamma_6(t-1)a_1 a_2\right\}
\end{aligned}
$$

	$d=1$	$d=2$	$d=3$	$d=4$
a_1	1	1	-1	-1
a_2	1	-1	1	-1

“GEE-Type” Estimating Equations for Model Parameters
(Lu, et al., 2016)

$$0 = \sum_{i=1}^{N} \sum_{d} \Big[I^{(d)}(A_{1i}, R_i, A_{2i}) \cdot W(R_i) \cdot \boldsymbol{D}^{(d)}(\boldsymbol{X}_i)^\top \cdot \boldsymbol{V}^{(d)}(\alpha)^{-1} \cdot \Big(\boldsymbol{Y}_i - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \gamma) \Big) \Big],$$

where

- d specifies an embedded DTR,
- $I^{(d)}(A_{1i}, R_i, A_{2i}) = \mathbb{1}_{\{A_{1i}=a_1\}} \left(R_i + (1 - R_i)\, \mathbb{1}_{\{A_{2i}=a_2\}} \right)$
- $W(R_i) = 2\left(R_i + 2(1 - R_i)\right)$
- $\boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \gamma) = E\left[\boldsymbol{Y}^{(d)} \mid \boldsymbol{X}_i\right]$
- $\boldsymbol{D}^{(d)}(\boldsymbol{X}_i) = \frac{\partial}{\partial(\boldsymbol{\eta}^\top, \gamma^\top)^\top} \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \gamma)$
- $\boldsymbol{V}^{(d)}(\alpha)$ is a working model for $\mathrm{Var}\left(\boldsymbol{Y}^{(d)} - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \gamma) \mid \boldsymbol{X}_i\right)$

Goal:

Develop a sample size formula for SMARTs with a continuous, repeated-measures outcome in which the primary aim is to compare two embedded DTRs at the end of the study.

Sample Size for an End-of-Study Comparison

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

where

- $\delta = \mathrm{E}[Y_2^{(d)} - Y_2^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_2^{(d)}) + \mathrm{Var}(Y_2^{(d')})\right)/2}$ is the targeted standardized effect size
- α is the desired type-I error
- $1-\beta$ is the desired power
- $\rho = \mathrm{cor}(Y_t, Y_{t'})$ for $t \neq t'$
- $r = P(R_i = 1)$

Sample Size for an End-of-Study Comparison

$$N \geq \underbrace{\frac{4\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\delta^2}}_{\text{Standard sample size for a 2-arm trial}} \cdot (1-\rho^2)\cdot(2-r)$$

where

- $\delta = \mathrm{E}[Y_2^{(d)} - Y_2^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_2^{(d)}) + \mathrm{Var}(Y_2^{(d')})\right)/2}$ is the targeted standardized effect size
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Sample Size for an End-of-Study Comparison

$$N \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\delta^2} \cdot \underbrace{(1-\rho^2)}_{\text{Deflation for repeated measures}} \cdot (2-r)$$

where

- $\delta = \mathrm{E}[Y_2^{(d)} - Y_2^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_2^{(d)}) + \mathrm{Var}(Y_2^{(d')})\right)/2}$ is the targeted standardized effect size
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Sample Size for an End-of-Study Comparison

$$N \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\delta^2} \cdot (1-\rho^2) \cdot \underbrace{\mathbf{(2-r)}}_{\text{Inflation for SMART design}}$$

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- $\delta = \mathrm{E}[Y_2^{(d)} - Y_2^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_2^{(d)}) + \mathrm{Var}(Y_2^{(d')})\right)/2}$ is the targeted standardized effect size
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- $r = P(R_i = 1)$

Sample Size for an End-of-Study Comparison

Table 1: Example sample sizes for comparison of two embedded DTRs. r $= 0.4$, $\alpha = 0.05$ (two-sided), and $1 - \beta = 0.8$.

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

Working Assumptions for Sample Size

1. *Constrained conditional variances.*
   1.1 $\text{Var}\left(Y_t^{(d)} \mid R^{(a_1)} = 0\right), \text{Var}\left(Y_t^{(d)} \mid R^{(a_1)} = 1\right) \leq \text{Var}\left(Y_t^{(d)}\right)$
   1.2 $\text{Cov}(Y_t^{(d)}, Y_2^{(d)} \mid R = 1) \leq \text{Cov}(Y_t^{(d)}, Y_2^{(d)} \mid R = 0)$ for all d and $t = 0, 1$.
2. *Exchangeable correlation structure.*

$$\text{Var}\left(\boldsymbol{Y}^{(d)}\right) = \sigma^2 \begin{bmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{bmatrix}$$

for all d.

Simulation Results

Target: $1-\beta$ = 0.8, $\alpha = 0.05$ (two-sided)

				Empirical power		
δ	$P(R=1)$	ρ	N	All satisfied	1.1 violated	1.2 violated
0.3	0.4	0	559	0.800	**0.790**	–
		0.3	508	0.803	**0.786**	**0.785**
		0.6	358	0.824	0.795	**0.779**
		0.8	201	0.825	**0.785**	0.803
	0.6	0	489	0.796	**0.773**	–
		0.3	445	0.797	**0.787**	**0.786**
		0.6	313	0.812	**0.783**	**0.766**
		0.8	176	0.827	**0.756**	**0.774**

Bolded results are significantly less than 0.8 at the 0.05 significance level.

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