Sample size considerations for comparing dynamic treatment regimes in a SMART with a longitudinal outcome

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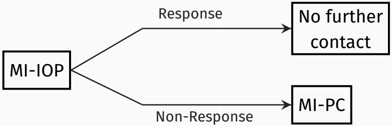
This is a question about a *sequence* of treatments.

Dynamic Treatment Regimes

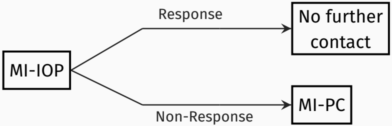
Dynamic treatment regimes (DTRs) operationalize clinical decision-making by recommending particular treatments to certain subsets of patients at specific times.



- **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.

. Chakraborty, B., and E. E. M. Moodie (2013). *Statistical Methods for Dynamic Treatment Regimes*.

Dynamic Treatment Regimes



We'll index a dynamic treatment regime with a triple

$$(a_1, a_{\mathrm{R}}, a_{\mathrm{NR}}).$$

This DTR is written

$$(\text{MI-IOP}, \text{No further contact}, \text{MI-PC}).$$

Sequential, Multiple-Assignment Randomized Trials

A **SMART** is one type of randomized trial design that can be used to answer questions at multiple stages of the development of a high-quality DTR.

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A **SMART** is one type of randomized trial design that can be used to answer questions at multiple stages of the development of a high-quality DTR.

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

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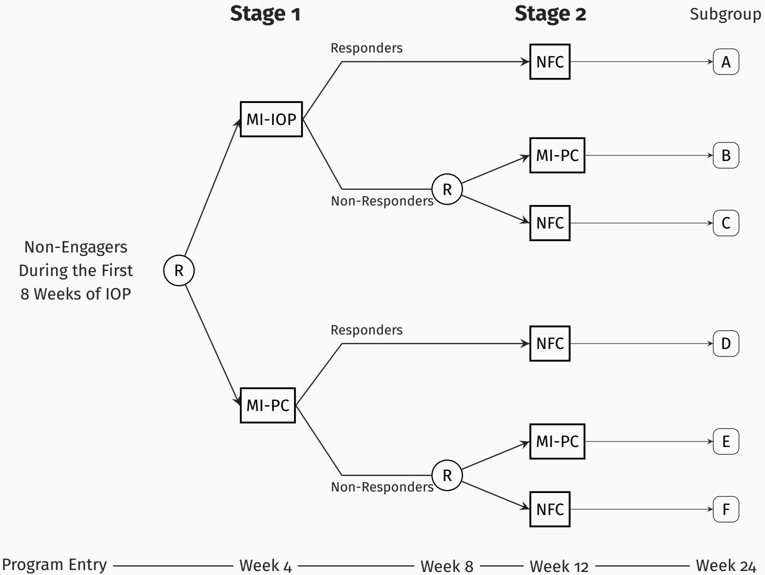
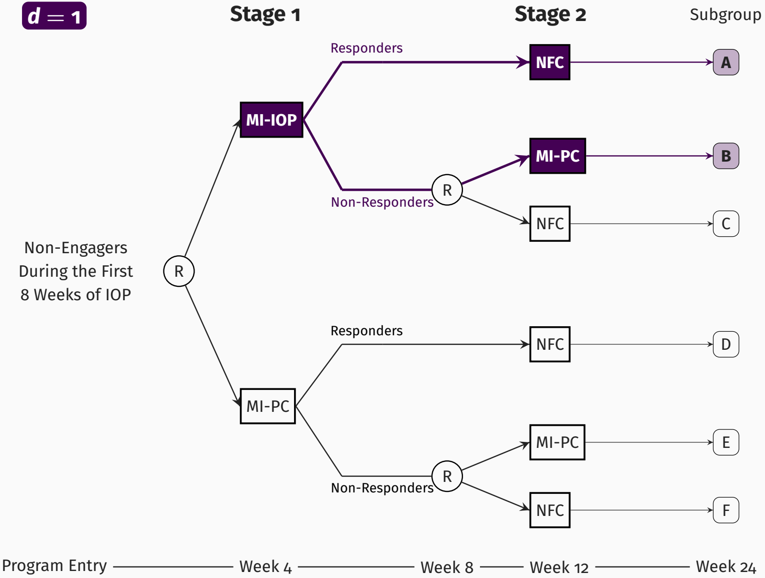


Four Embedded DTRs in ENGAGE



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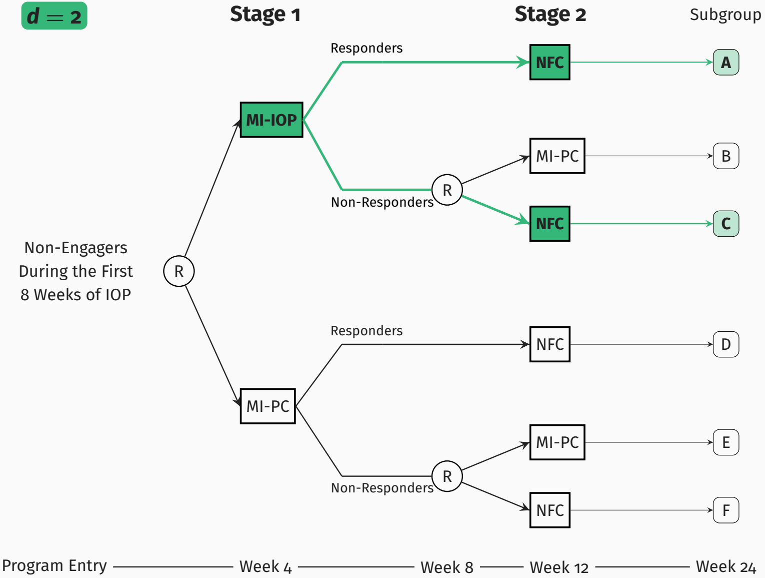

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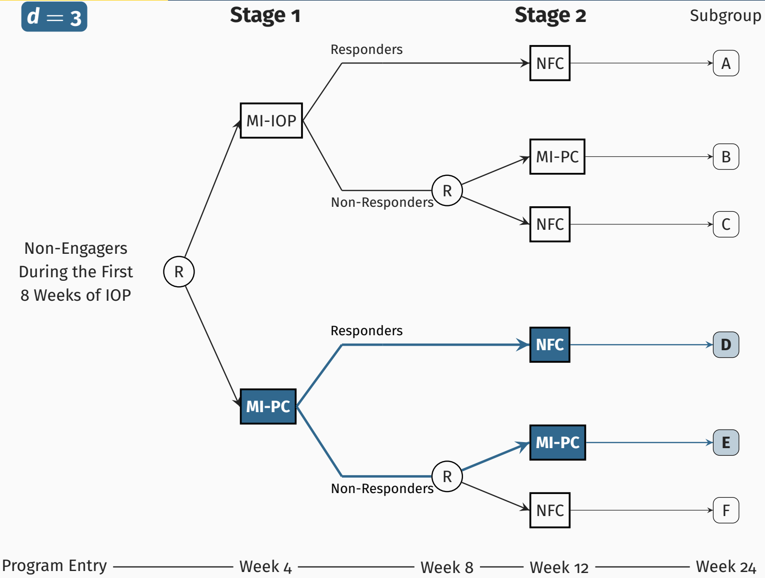

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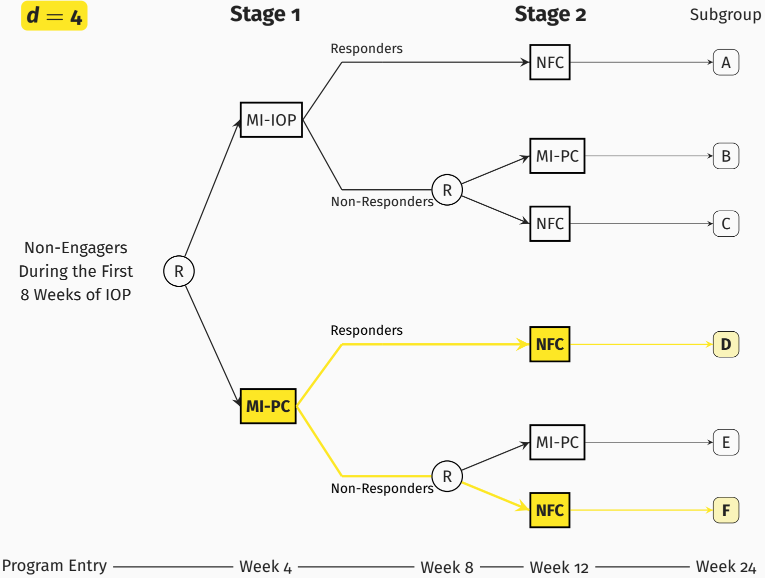
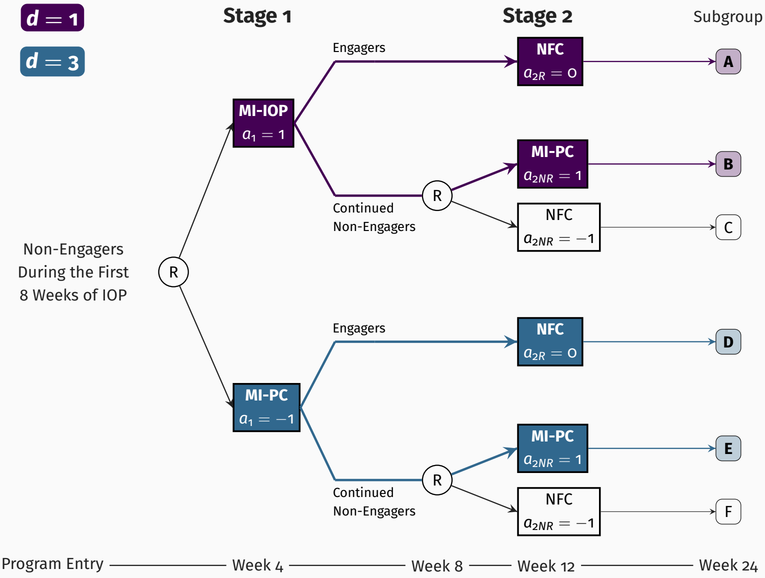


A common primary aim in a SMART is the comparison of two embedded DTRs **using a continuous longitudinal outcome at the end of the study**.

$$E\left[Y_{t_{\max}}^{(1,a_{2R},a_{2NR})} - Y_{t_{\max}}^{(-1,a'_{2R},a'_{2NR})}\right]$$

Primary Aim



d = 1
d = 3
Stage 1
Stage 2
Subgroup
Engagers
NFC
$a_{2R} = 0$
A
MI-IOP
$a_1 = 1$
MI-PC
$a_{2NR} = 1$
B
R
Continued
Non-Engagers
NFC
$a_{2NR} = -1$
C
Non-Engagers
During the First
8 Weeks of IOP
R
Engagers
NFC
$a_{2R} = 0$
D
MI-PC
$a_1 = -1$
MI-PC
$a_{2NR} = 1$
E
R
Continued
Non-Engagers
NFC
$a_{2NR} = -1$
F
Program Entry
Week 4
Week 8
Week 12
Week 24

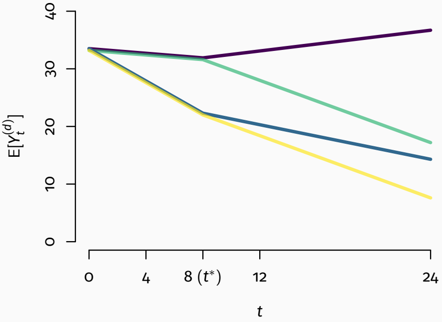
Observed Data

$$\left(Y_0,\ A_{1,i},\ \boldsymbol{Y}_{[0<t\leq t^*],i},\ R_i,\ A_{2,i},\ \boldsymbol{Y}_{[t>t^*],i}\right)$$

For the ith participant, $i = 1, \ldots, n$,

- $A_{1,i} \in \{-1, 1\}$ indicates the randomly assigned first-stage treatment
- $R_i = \mathbb{1}\left\{i\text{th participant responded to first-stage treatment}\right\}$
- $A_{2,i} \in \{-1, 0, 1\}$ indicates the randomly assigned second-stage treatment (± 1 if re-randomized, 0 otherwise)
- $\boldsymbol{Y}_i = \left\{Y_{1,i}, \ldots, Y_{T,i}\right\}$ is the vector of continuous outcomes observed throughout the study
- t^* is the timepoint immediately prior to second randomization

An Example Model for a Continuous Longitudinal Outcome in ENGAGE (Lu et al. 2016)



	$d=1$	$d=2$	$d=3$	$d=4$
a_1	1	1	-1	-1
a_{2R}	0	0	0	0
a_{2NR}	1	-1	1	-1

$$
\begin{aligned}
\mathrm{E}\left[Y_t^{(d)}\right] &:= \boldsymbol{\mu}^{(d)}(\boldsymbol{\beta}) \\
&= \beta_0 \\
&\quad + \mathbb{1}\left\{t \le t^*\right\}\left\{\beta_1 t + \beta_2 a_1 t\right\} \\
&\quad + \mathbb{1}\left\{t > t^*\right\}\left\{t^*\beta_1 + t^*\beta_2 a_1\right. \\
&\qquad + \beta_3(t-t^*) + \beta_4(t-t^*)a_1 \\
&\qquad + \beta_5(t-t^*)a_{2NR} \\
&\qquad \left. + \beta_6(t-t^*)a_1 a_{2NR}\right\}
\end{aligned}
$$

"GEE-Type" Estimating Equations for Model Parameters

$$0 = \sum_{i=1}^{N} \sum_{d} \Bigg[\underbrace{\frac{I^{(d)}(A_{1,i}, R_i, A_{2,i})}{P(A_{1,i} = a_1)P(A_{2,i} = a_2 \mid A_{1,i} = a_1, R_i)}}_{W^{(d)}(A_{1,i}, R_i, A_{2,i})} \cdot \left(\boldsymbol{D}^{(d)}\right)^{\top} \cdot \boldsymbol{V}^{(d)}(\boldsymbol{\tau})^{-1} \cdot \left(\boldsymbol{Y}_i - \boldsymbol{\mu}^{(d)}(\boldsymbol{\beta})\right) \Bigg],$$

where

- d specifies an embedded DTR,
- $W^{(d)}(A_{1,i}, R_i, A_{2,i}) = \mathbb{1}\{A_{1,i} = a_1\} \left(2R_i + 4(1 - R_i)\mathbb{1}\{A_{2,i} = a_2\}\right)$
- $\boldsymbol{D}^{(d)} = \frac{\partial}{\partial \boldsymbol{\beta}^{\top}} \boldsymbol{\mu}^{(d)}(\boldsymbol{\beta})$
- $\boldsymbol{V}^{(d)}(\boldsymbol{\tau})$ is a working model for $\mathbf{Var}\left(\boldsymbol{Y}^{(d)} - \boldsymbol{\mu}^{(d)}(\boldsymbol{\beta})\right)$

- Lu, X., et al. (2016). *Stat. Med.*

Goal:
For this analysis, develop a sample size formula for SMARTs with a continuous longitudinal outcome in which the primary aim is to compare, at end-of-study, two embedded DTRs which recommend different first-stage treatments.

Hypotheses and Estimand

- Using the GEE-type analysis, we want to test

$$H_0 : \boldsymbol{c}^\top \boldsymbol{\beta} = 0$$

  against an alternative of the form $H_1 : \boldsymbol{c}^\top \boldsymbol{\beta} = \Delta$.
- We choose $\boldsymbol{c}$ such that

$$\boldsymbol{c}^\top \boldsymbol{\beta} = \mathrm{E}\left[Y_2^{(1, a_{2R}, a_{2NR})} - Y_2^{(-1, a'_{2R}, a'_{2NR})}\right]$$

A Test Statistic

We use a 1-degree of freedom Wald test with test statistic

$$Z = \frac{\sqrt{n}\boldsymbol{c}^\top \hat{\beta}}{\sigma_c},$$

where $\sigma_c^2 = \text{Var}\left(\boldsymbol{c}^\top \hat{\beta}\right) = \boldsymbol{c}^\top \boldsymbol{B}^{-1}\hat{\boldsymbol{M}}\boldsymbol{B}^{-1}\boldsymbol{c}$ and

$$\boldsymbol{B} := \text{E}\left[\sum_{d \in \mathcal{D}} W^{(d)}\left(A_{1,i}, R_i, A_{2,i}\right)\left(\boldsymbol{D}^{(d)}\right)^\top \boldsymbol{V}^{(d)}(\boldsymbol{\tau})^{-1}\boldsymbol{D}^{(d)}\right]$$

$$\boldsymbol{M} := \text{E}\left[\left(\sum_{d \in \mathcal{D}} W^{(d)}\left(A_{1,i}, R_i, A_{2,i}\right)\boldsymbol{D}^{(d)}\boldsymbol{V}^{(d)}(\boldsymbol{\tau})^{-1}\left(\boldsymbol{Y}_i - \boldsymbol{\mu}^{(d)}(\beta)\right)\right)^{\otimes 2}\right]$$

Context:

- Three timepoints
- Randomization probability 0.5
- Exchangeable correlation structure
- Some working assumptions (to come)

Sample Size for an End-of-Study Comparison

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

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
- $1-\gamma$ 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

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

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

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

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

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

where

- $\delta = \text{E}[Y_2^{(d)} - Y_2^{(d')}]/\sqrt{\left(\text{Var}(Y_2^{(d)}) + \text{Var}(Y_2^{(d')})\right)/2}$ 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 $1 - \gamma = 0.8$.

	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

Working Assumptions for Sample Size

1. *Response is uncorrelated with products of first-stage residuals.* For any $t_i \leq t_j \leq t^*$,

$$\text{Cov}\left(R^{(a_1)}, \left(Y_{t_i}^{(d)} - \mu_{t_i}^{(d)}\right)\left(Y_{t_j}^{(d)} - \mu_{t_j}^{(d)}\right)\right) = 0$$

- Oetting, A. I., et al. (2011).

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2. *Constrained conditional covariances.*

   2.1 $\text{E}\left[\left(Y_2^{(d)} - \mu_2^{(d)}\right)^2 \mid R^{(a_1)} = 0\right] \leq \text{Var}\left(Y_2^{(d)}\right)$

   2.2 $\text{Cov}(Y_t^{(d)}, Y_2^{(d)} \mid R = 1) \leq \text{Cov}(Y_t^{(d)}, Y_2^{(d)} \mid R = 0)$ for all d and $t = 0, 1$.

. Oetting, A. I., et al. (2011).

Working Assumptions for Sample Size

3. *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: $1-\gamma$ = 0.8, $\alpha = 0.05$ (two-sided)

δ	$P(R=1)$	ρ	N	Empirical power: All satisfied	1 violated	2.1 violated	2.2 violated
0.3	0.4	0	559	0.801	0.778*	0.803	–
		0.3	508	0.804	0.800	0.797	0.798
		0.6	358	0.817	0.807	0.759*	0.788
		0.8	201	0.836	0.809	–	0.792
	0.6	0	489	0.804	0.736*	0.810	–
		0.3	445	0.797	0.758*	0.795	0.780*
		0.6	313	0.824	0.793	0.752*	0.770*
		0.8	176	0.845	0.754*	–	0.776*

* Result is significantly less than 0.8 at the 0.05 significance level.

Extension to More than Three Timepoints

- A work in progress!
- Challenges:
    - When should we add timepoints? First stage? Second stage? Both?
    - How do we generalize our working assumptions to general covariance matrices?
    - Relationship between power and ρ appears to be highly dependent on working correlation structure

Article

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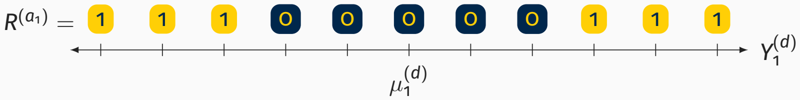
Extra Slides

Working Assumptions for Sample Size

1. *Response is uncorrelated with products of first-stage residuals.* For any $t_i \leq t_j \leq t^*$,

$$\text{Cov}\left(R^{(a_1)}, \left(Y_{t_i}^{(d)} - \mu_{t_i}^{(d)}\right)\left(Y_{t_j}^{(d)} - \mu_{t_j}^{(d)}\right)\right) = 0$$

Intuition: If this is not true, the relationship between, say $Y_1^{(d)}$ and R might look like this:



Two Definitions of Response