# Sample Size Considerations for Comparing Dynamic Treatment Regimens in a Sequentially-Randomized Trial with a Continuous Longitudinal Outcome

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# Motivating Example: The ENGAGE Study

In treating alcohol- and cocaine-dependent patients, there is a question as to how best to re-engage individuals who do not engage in treatment.

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- McKay, J. R., et al. (2015). *J. Consult. Clin. Psychol.*

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

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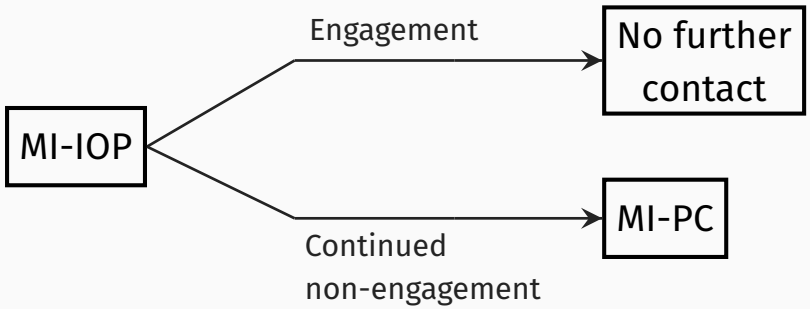
# Dynamic Treatment Regimens

**Dynamic treatment regimens** (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 **I**ntensive **O**utpatient **P**rogram
- **MI-PC**: 2 motivational interviews to engage **P**atient in treatment of their **C**hoice.

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

# 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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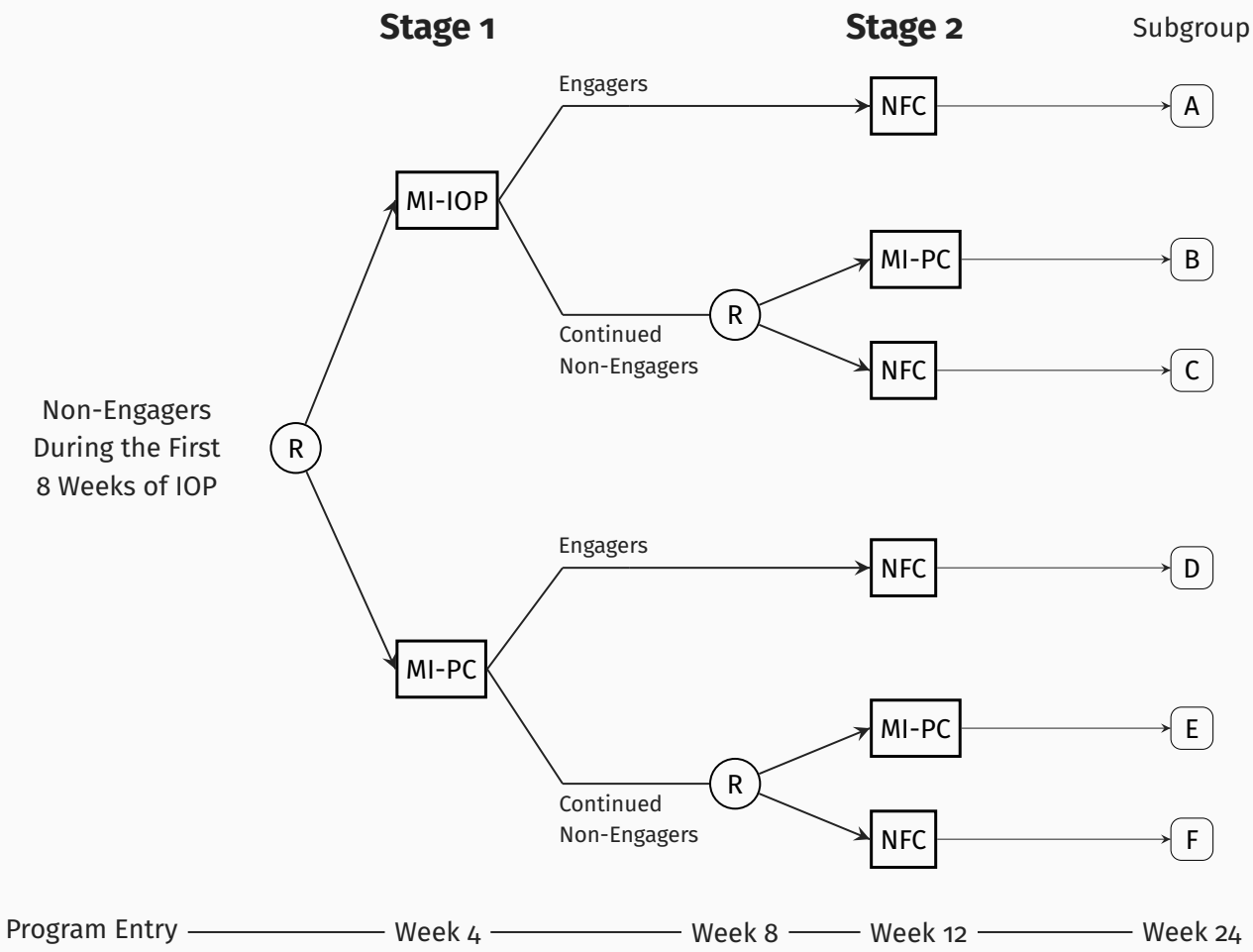


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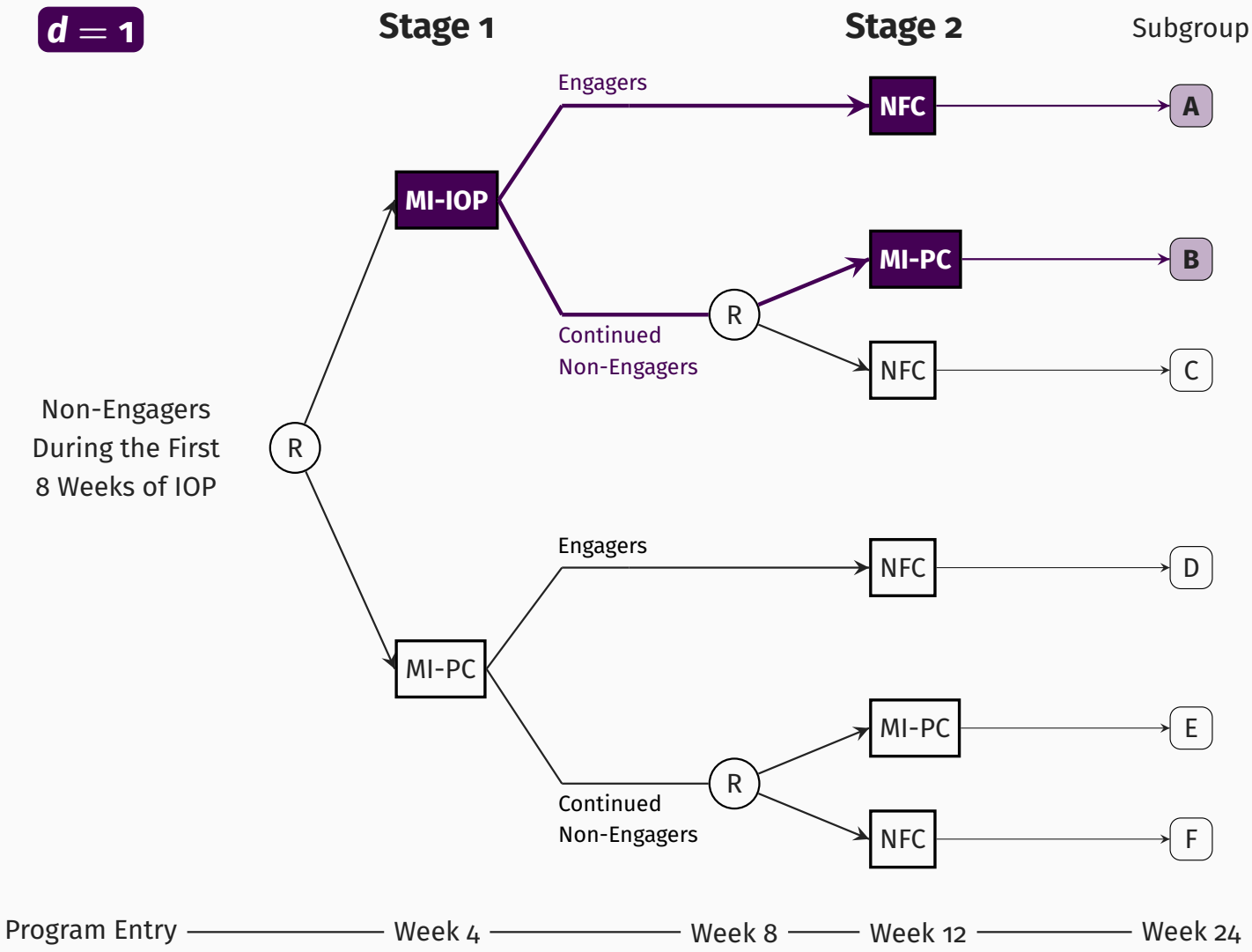
# Four Embedded DTRs in ENGAGE



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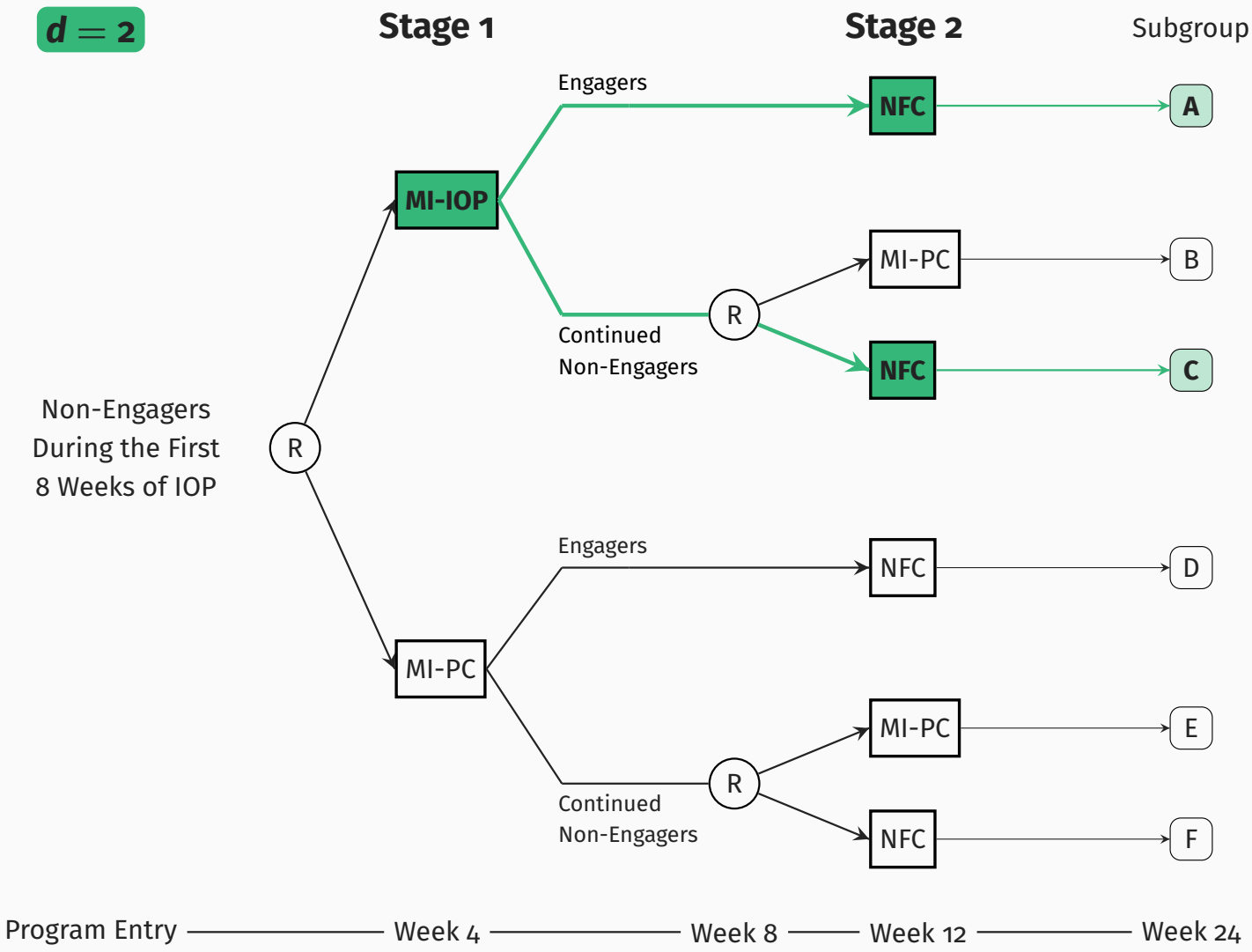

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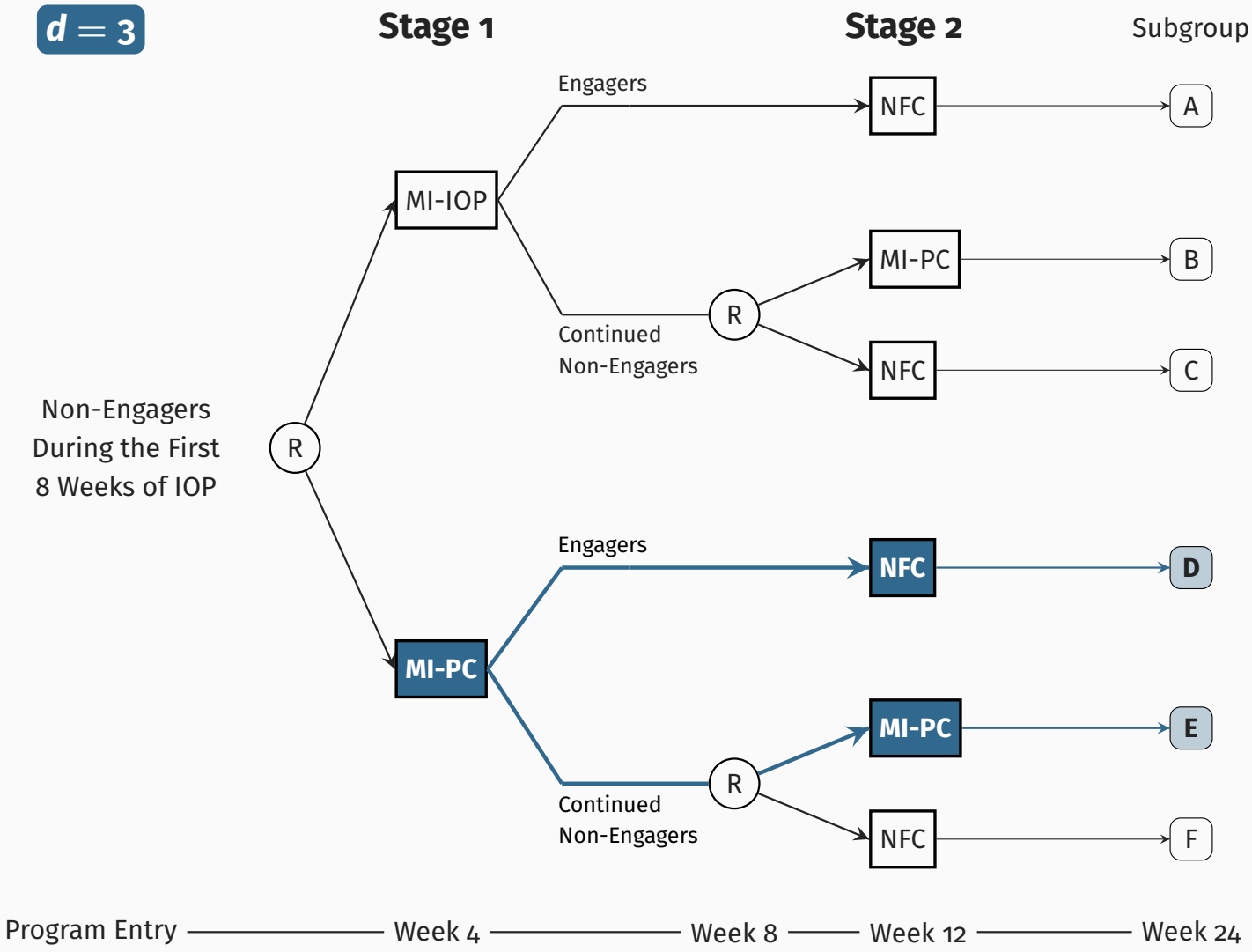

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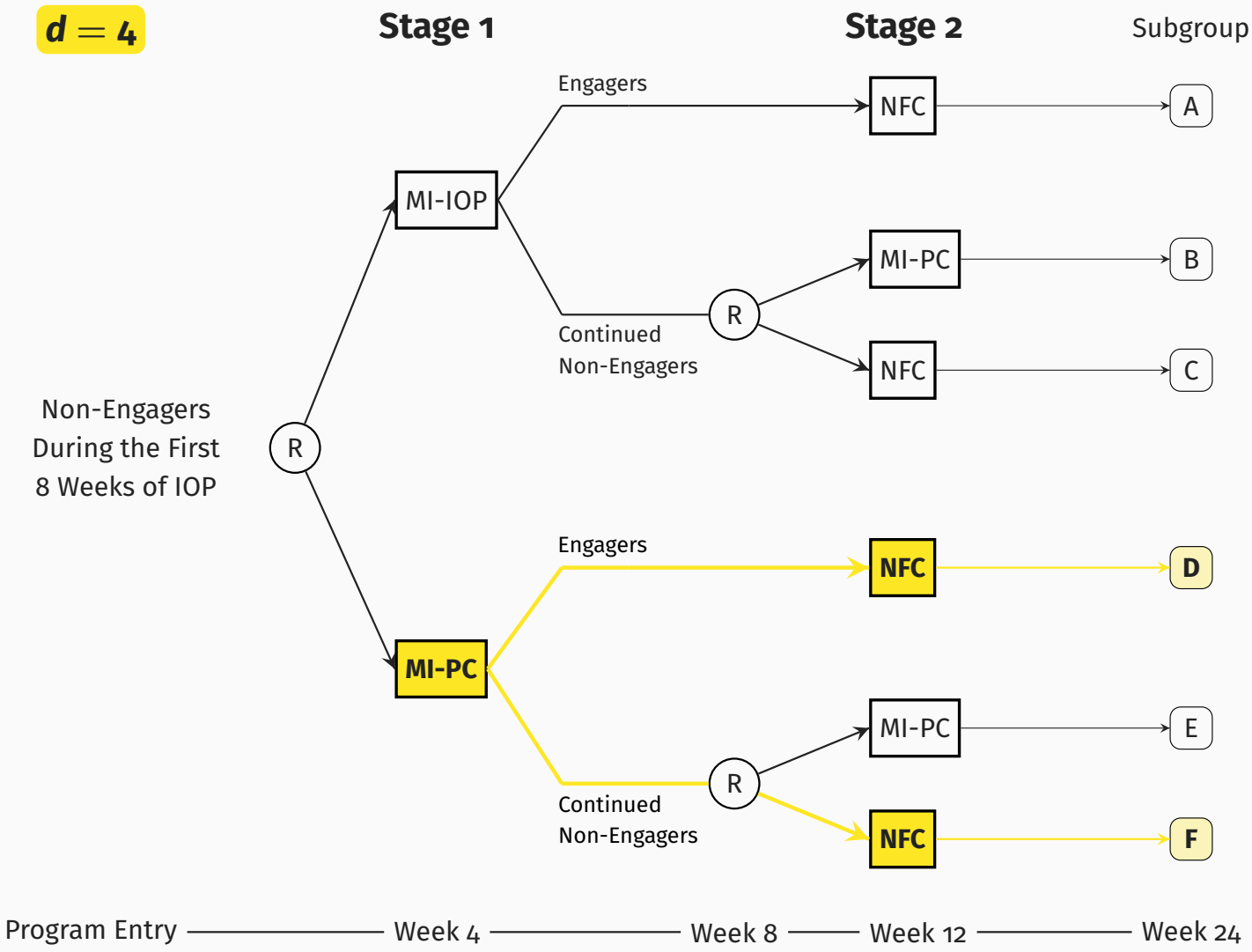
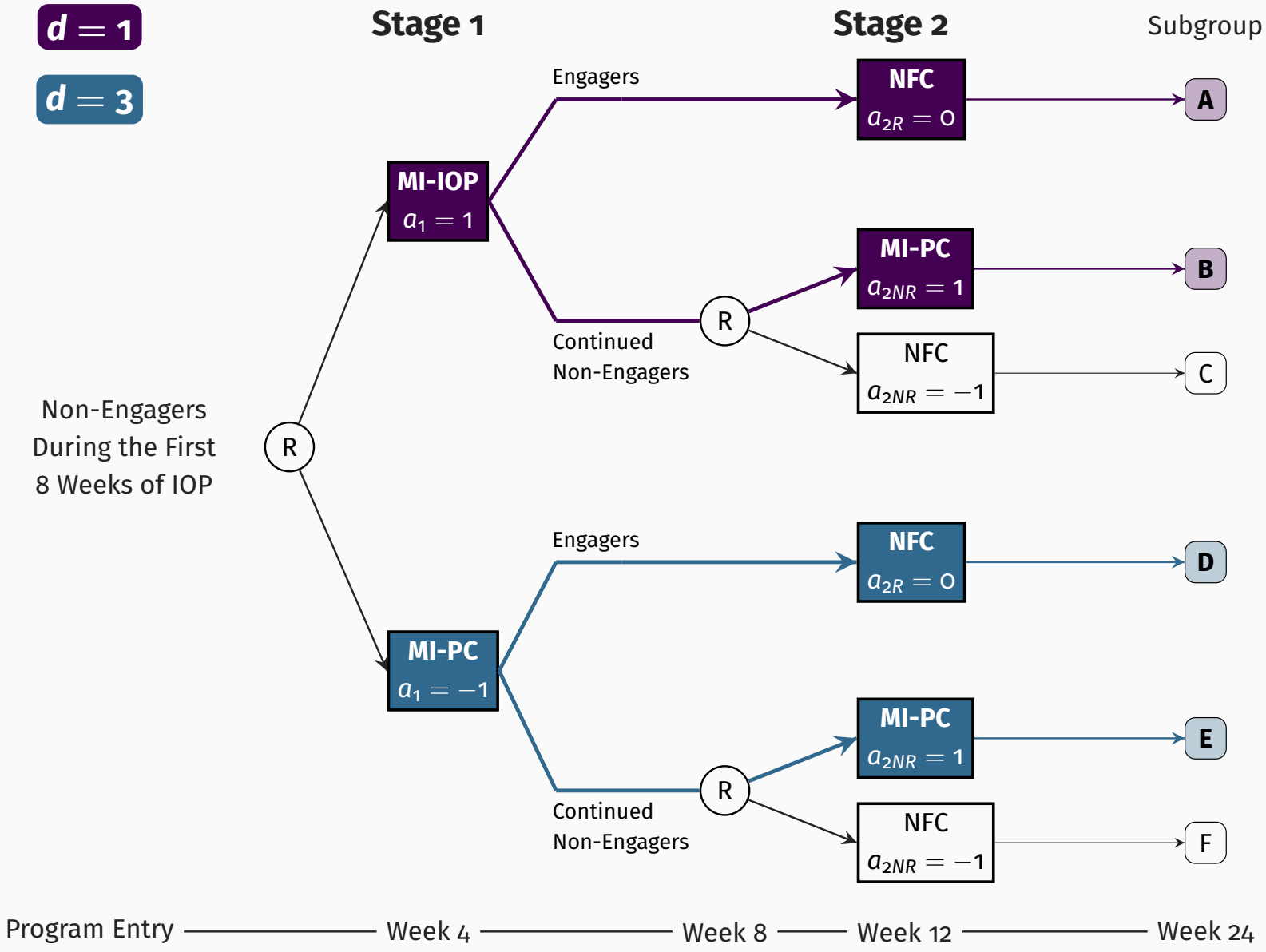
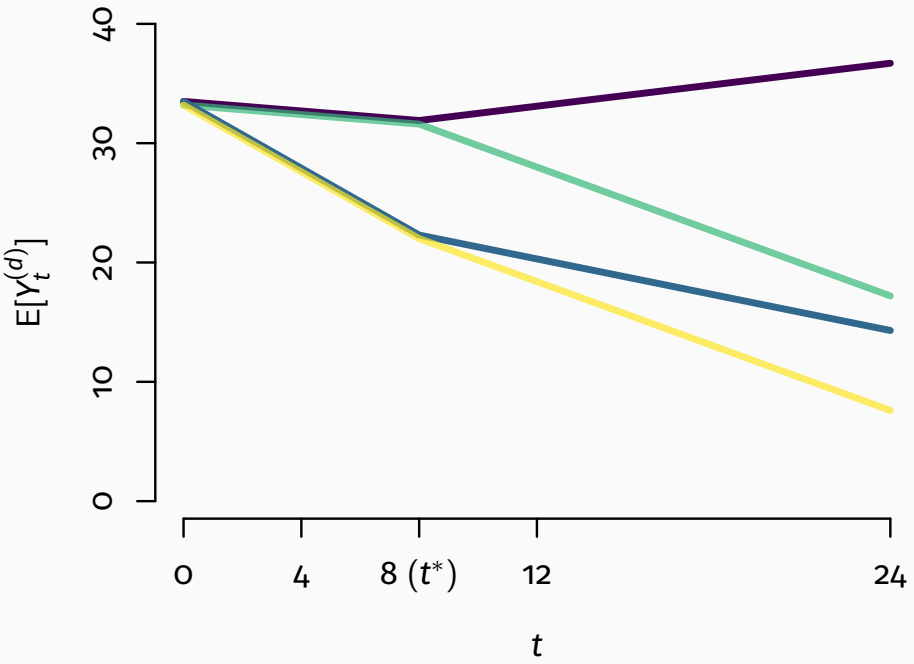


**A common primary aim in a SMART**
is the comparison of two embedded DTRs using a continuous outcome collected at the end of the study.

# Primary Aim


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

# 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 |

$$
\begin{aligned}
\mathrm{E}\left[Y_t^{(d)} \mid \boldsymbol{X}\right] &:= \mu^{(d)}(\boldsymbol{X}_i; \eta, \gamma) \\
&= \eta^\top \boldsymbol{X}_i + \gamma_0 \\
&\quad + \mathbb{1}\{t \le t^*\}\{\gamma_1 t + \gamma_2 a_1 t\} \\
&\quad + \mathbb{1}\{t > t^*\}\{t^*\gamma_1 + t^*\gamma_2 a_1 \\
&\qquad + \gamma_3(t - t^*) + \gamma_4(t - t^*)a_1 \\
&\qquad + \gamma_5(t - t^*)a_{2NR} \\
&\qquad + \gamma_6(t - t^*)a_1 a_{2NR}\}
\end{aligned}
$$

# “GEE-Type” Estimating Equations for Model Parameters

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

where

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

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

**Goal:**
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.

# 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
- $\alpha$ 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

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# Sample Size for an End-of-Study Comparison

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

where

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- $\alpha$ is the desired type-I error
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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 | | |
|---|---|---|---|
| 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 $$\text{E}\left[\left(Y_2^{(d)} - \mu_2^{(d)}\right)^2 \mid R^{(a_1)} = 0\right] \leq \text{Var}\left(Y_2^{(d)}\right)$$

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

| $\delta$ | $P(R = 1)$ | $\rho$ | $N$ | 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.

## Funding

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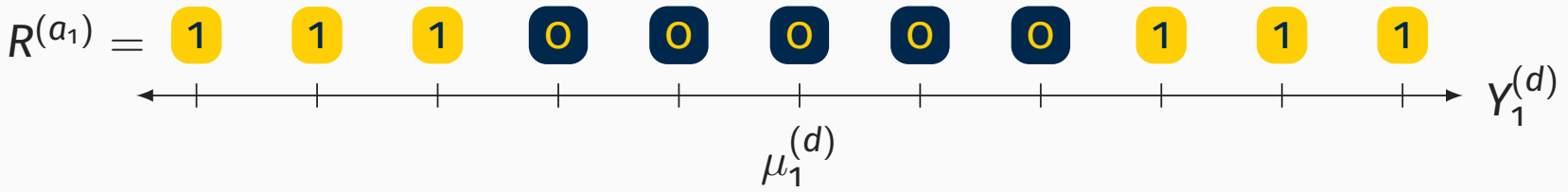
# Extra Slides

# 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

$$R^{(a_1)} = \mathbb{1}\left\{\left(Y_1^{(d)}\right)^2 > 4.7\right\}$$

$$\text{Cov}\left(R^{(a_1)}, \left(Y_1^{(d)} - \mu_1^{(d)}\right)^2\right) = 3.673$$

$$R^{(a_1)} = \mathbb{1}\left\{Y_1^{(d)} > 0.7\right\}$$

$$\text{Cov}\left(R^{(a_1)}, \left(Y_1^{(d)} - \mu_1^{(d)}\right)^2\right) = 0.941$$