Design Considerations for Comparing Dynamic Treatment Regimens in a Longitudinal SMART

Nicholas J. Seewald

Department of Statistics
University of Michigan

Joint with D. Almirall

ENAR 2020
23 March 2020

Motivating Example: The ENGAGE Study

Patients with alcohol- and cocaine-related substance use disorders often disengage from treatment at high rates. How should clinicians best re-engage them?

. McKay, J. R., et al. (2015). *Journal of Consulting and Clinical Psychology*.

Motivating Example: The ENGAGE Study

Patients with alcohol- and cocaine-related substance use disorders often disengage from treatment at high rates. How should clinicians best re-engage them?

For these individuals, should we attempt to re-engage them in their original treatment, or offer them a choice of treatment modality?

. McKay, J. R., et al. (2015). *Journal of Consulting and Clinical Psychology*.

Motivating Example: The ENGAGE Study

Patients with alcohol- and cocaine-related substance use disorders often disengage from treatment at high rates. How should clinicians best re-engage them?

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?

. McKay, J. R., et al. (2015). *Journal of Consulting and Clinical Psychology*.

Motivating Example: The ENGAGE Study

Patients with alcohol- and cocaine-related substance use disorders often disengage from treatment at high rates. How should clinicians best re-engage them?

For these individuals, should we attempt to re-engage them in their original treatment, or offer them a choice of treatment modality?

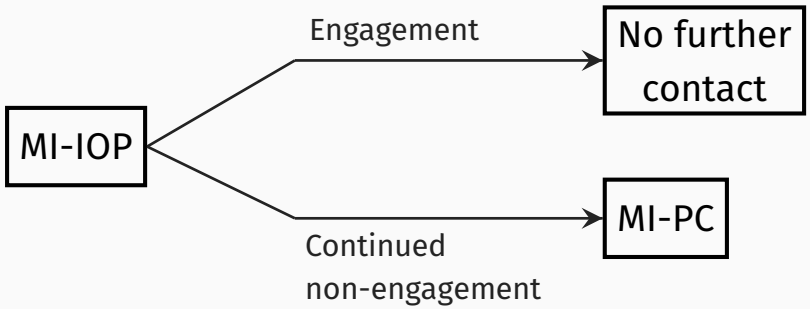
What do we do if that doesn't work?

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

. McKay, J. R., et al. (2015). *Journal of Consulting and Clinical Psychology*.

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 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*.

Sequential, Multiple-Assignment Randomized Trials

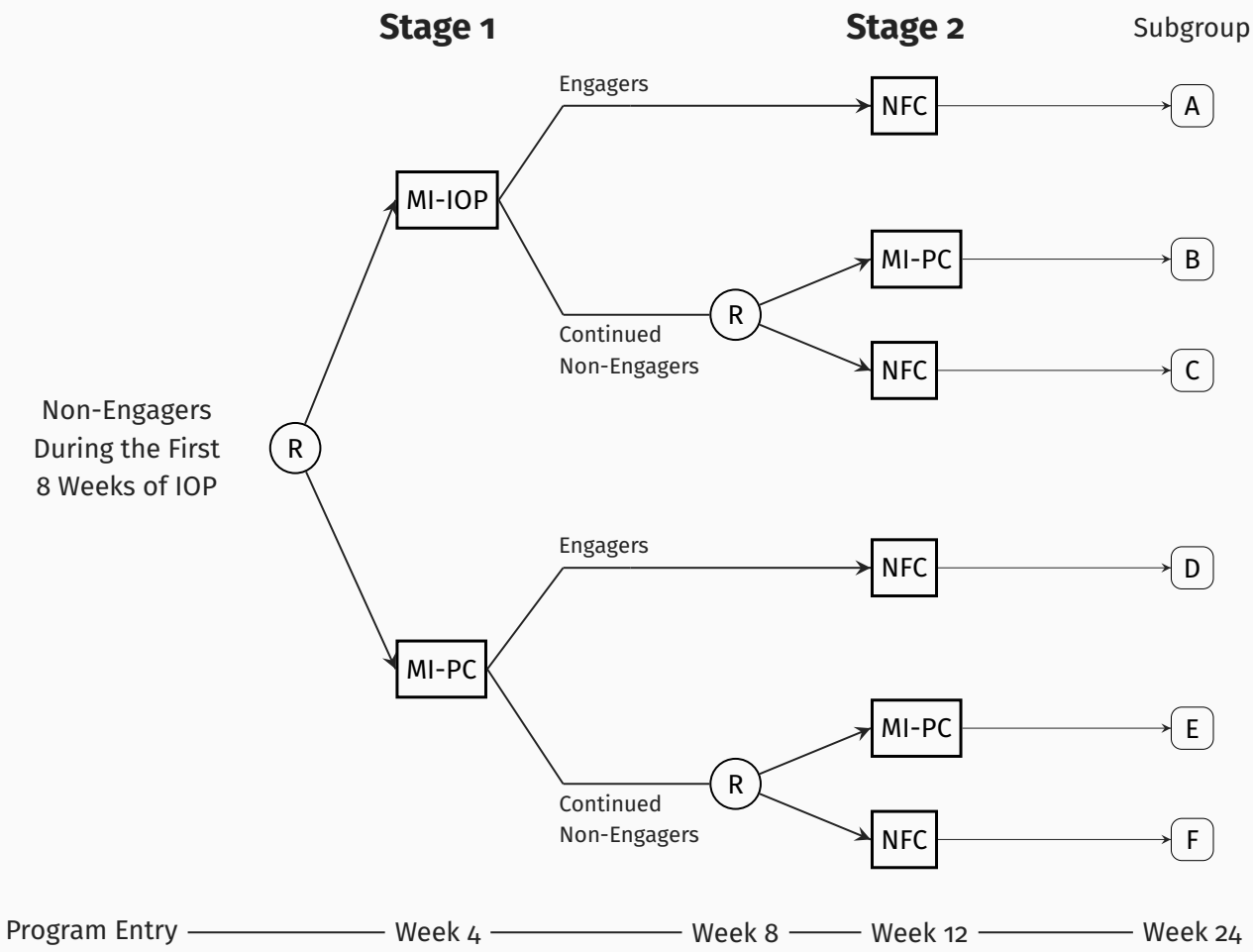
A **SMART** is one type of randomized trial design that can be used to answer questions at multiple stages of the development of a high-quality DTR.

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.

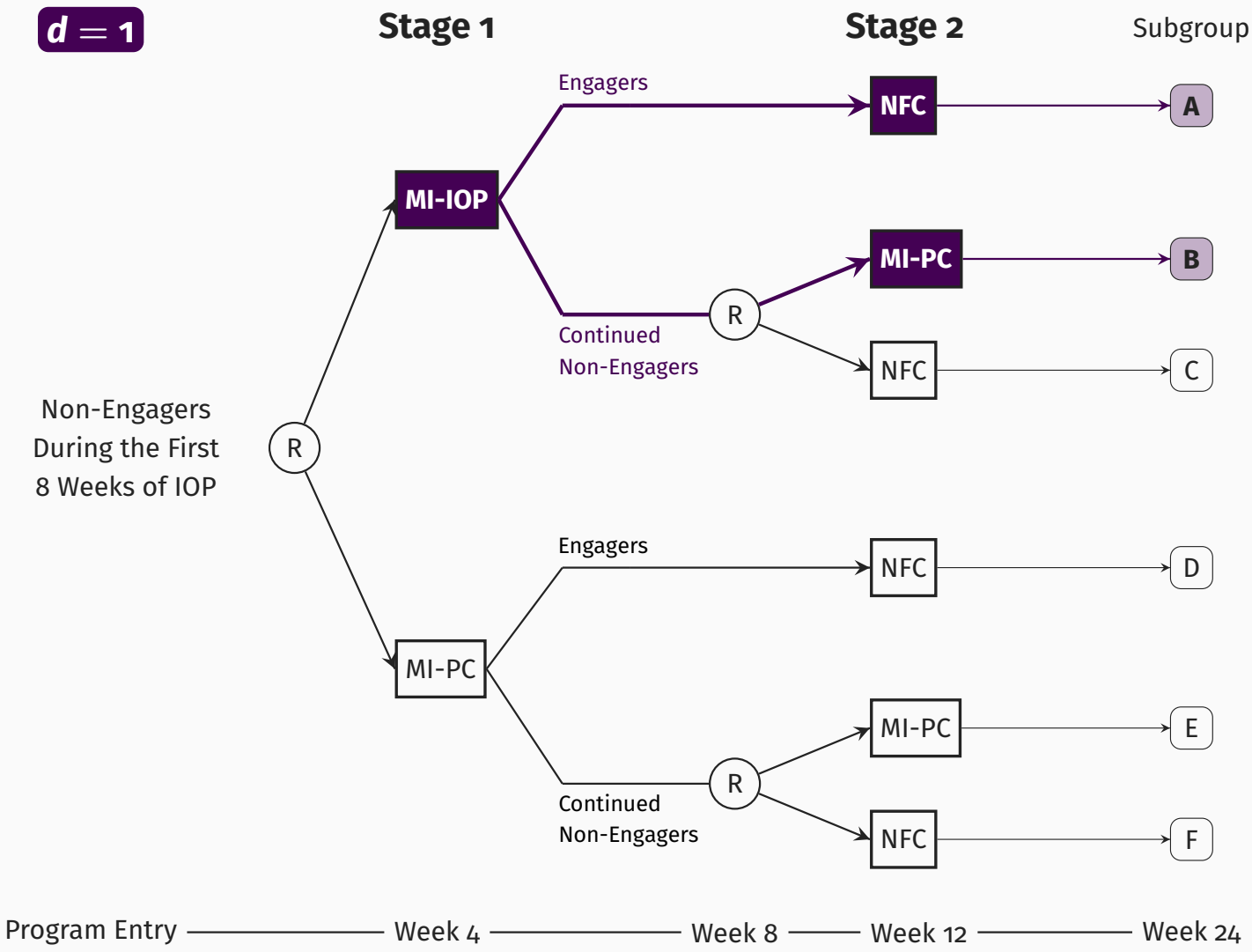
The key feature of a SMART is that some (or all) participants are randomized *more than once*.

Motivating Example: The ENGAGE Study

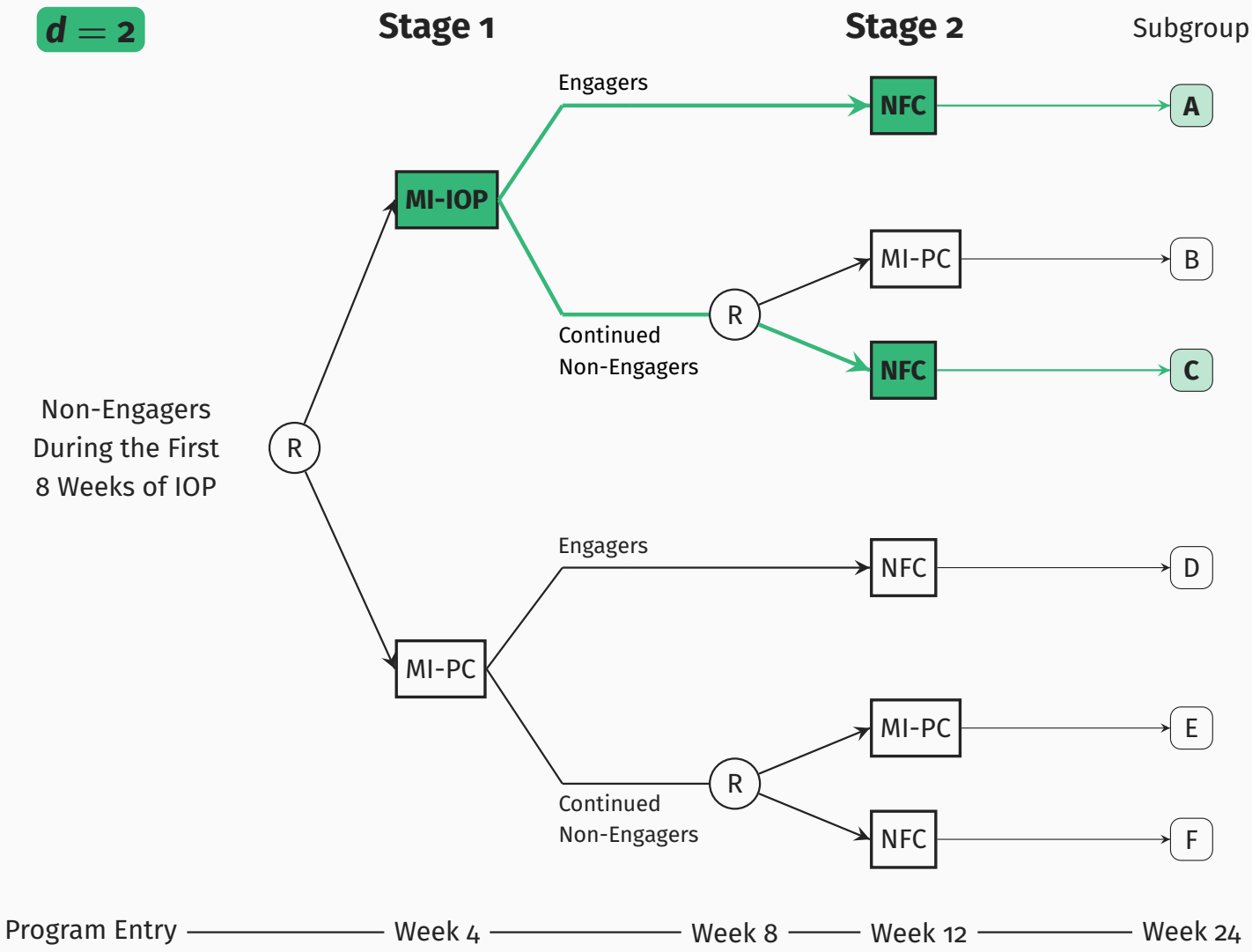


- McKay, J. R., et al. (2015). *Journal of Consulting and Clinical Psychology*.

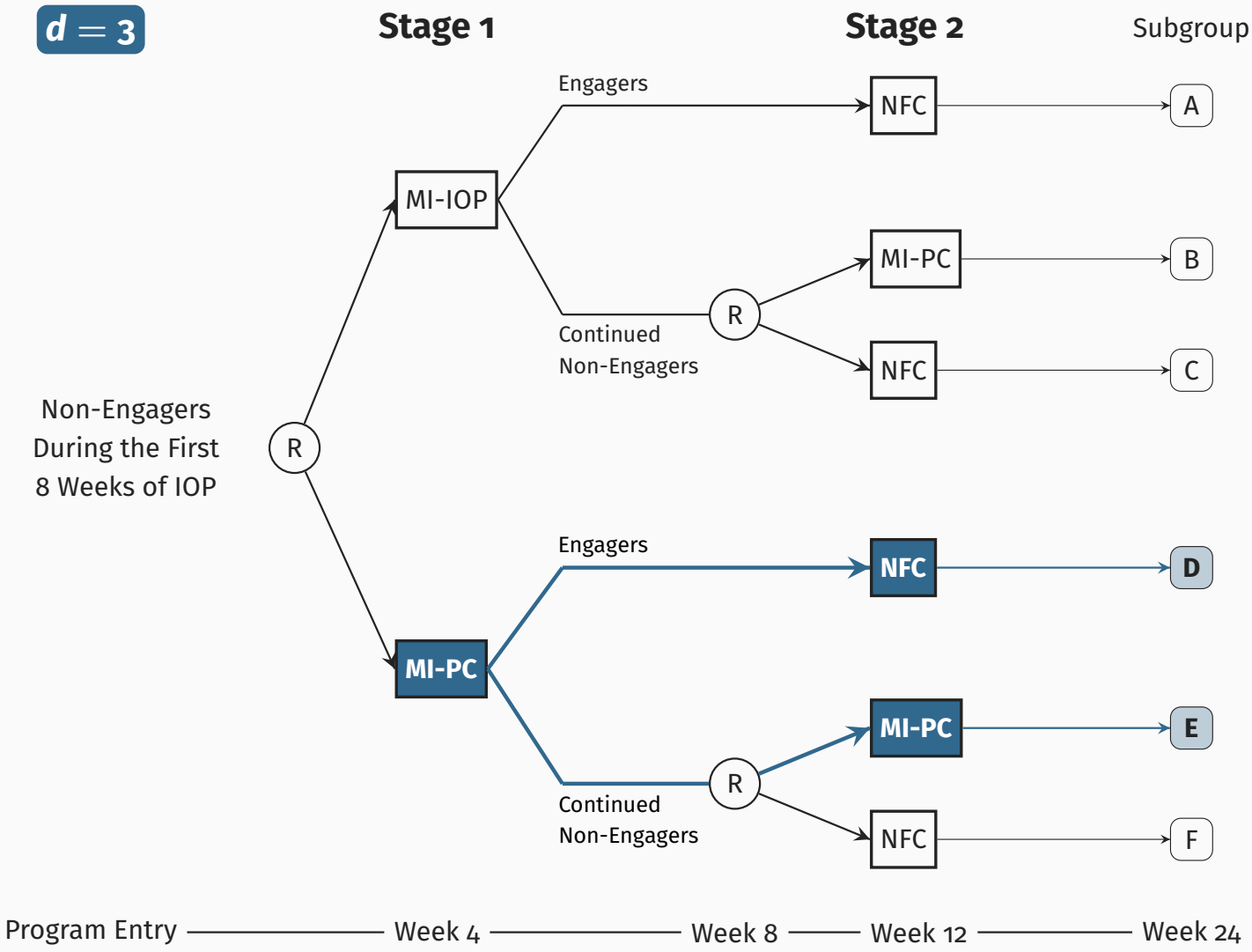
Four Embedded DTRs in ENGAGE



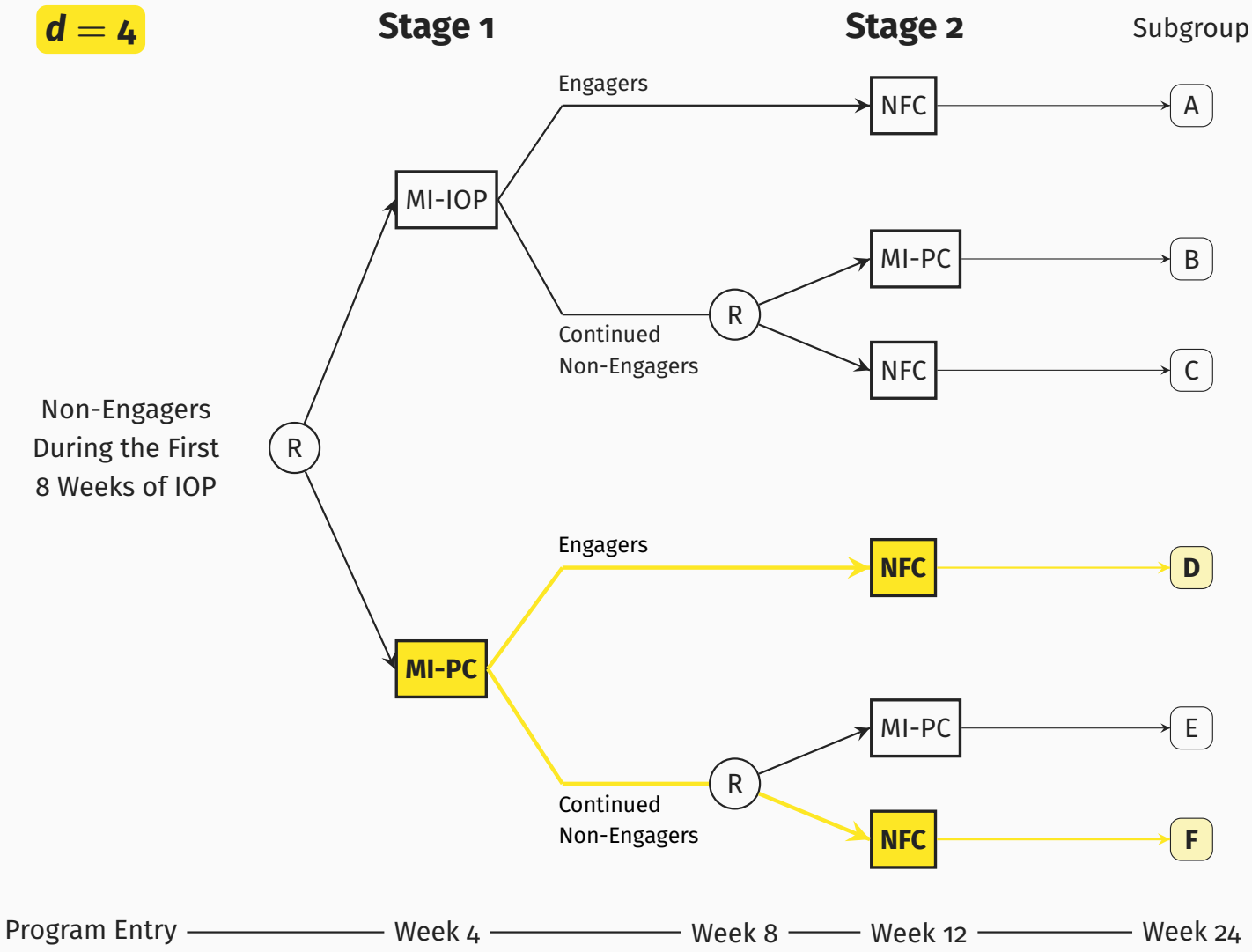
Four Embedded DTRs in ENGAGE



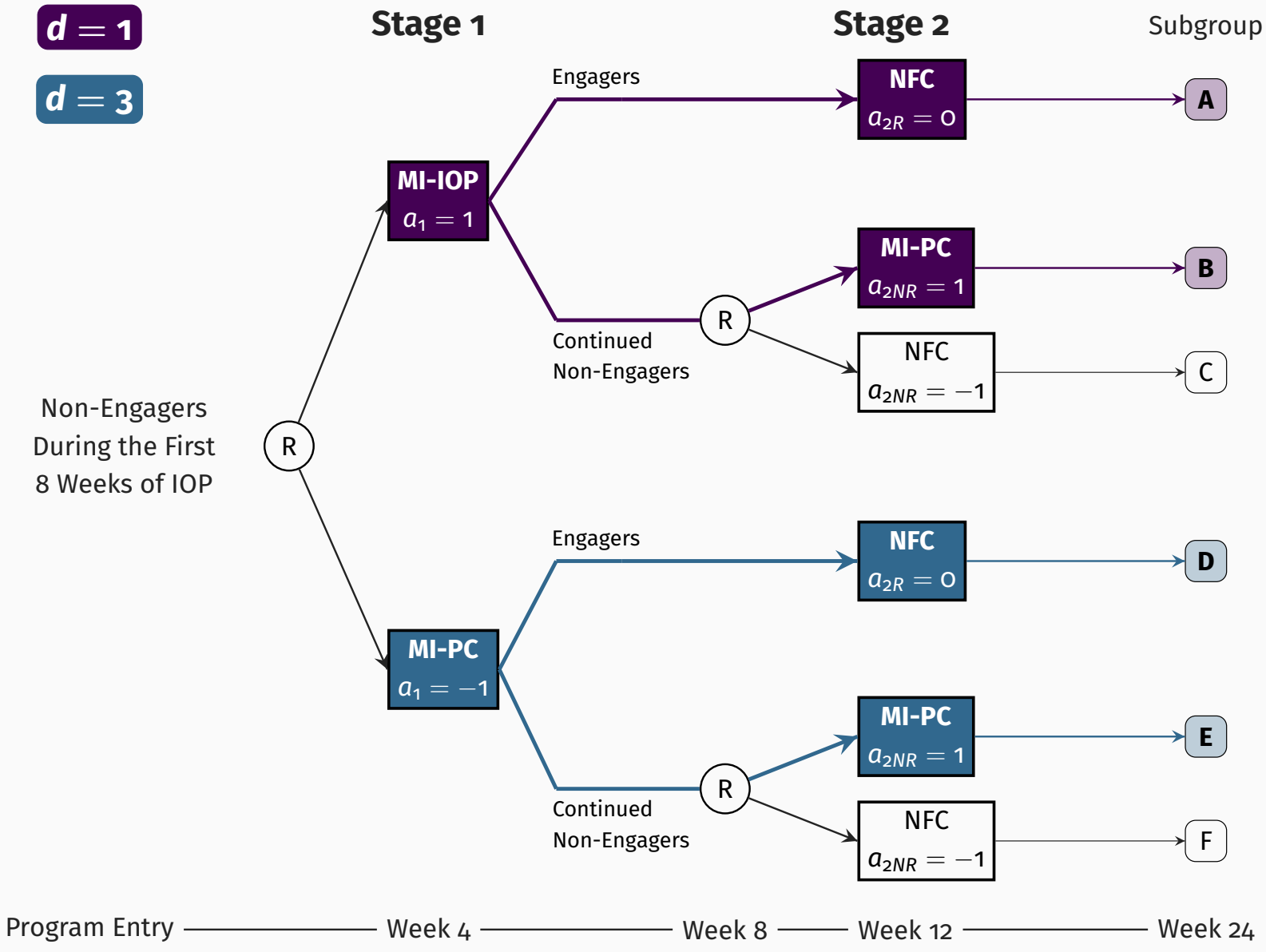
Four Embedded DTRs in ENGAGE



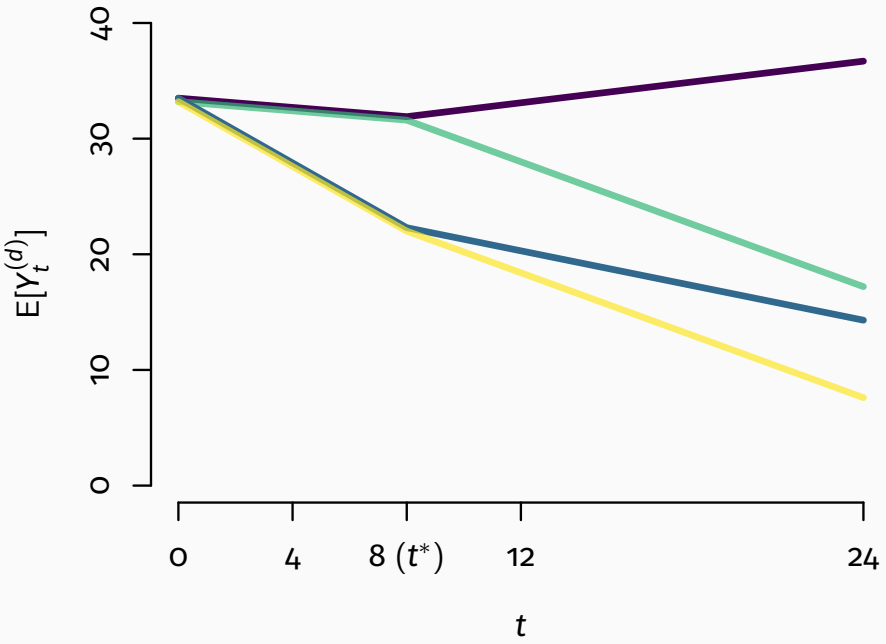
Four Embedded DTRs in ENGAGE



Primary Aim


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

Example Model: Continuous Longitudinal Outcome in ENGAGE



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

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

. Lu, X., et al. (2016). *Statistics in Medicine*.

“GEE-Type” Estimating Equations for Model Parameters

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

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

. Lu, X., et al. (2016). *Statistics in Medicine*.

Variance of Parameter Estimates

- Call the solution to the estimating equations $\hat{\beta}$
- Under usual regularity conditions:
  - $\hat{\beta} \xrightarrow{p} \beta^*$
  - $\sqrt{n}\left(\hat{\beta} - \beta^*\right) \Rightarrow \mathcal{N}\left(\mathbf{o}, \boldsymbol{B}^{-1}\boldsymbol{M}\boldsymbol{B}^{-1}\right)$

where

$$\boldsymbol{B} := \mathrm{E}\left[\sum_{d\in\mathcal{D}} W^{(d)}\left(A_1, R, A_2\right)\left(\boldsymbol{D}^{(d)}\right)^{\top}\left(\boldsymbol{V}^{(d)}(\tau)\right)^{-1}\boldsymbol{D}^{(d)}\right]$$

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

. Vaart, A. W. van der (1998). *Asymptotic statistics*.

Goal

Goal: Develop a tractable sample size formula for the test

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

Goal

Goal: Develop a tractable sample size formula for the test

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

We choose $\boldsymbol{c}$ such that

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

Goal

Goal: Develop a tractable sample size formula for the test

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

We choose $\boldsymbol{c}$ such that

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

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

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

where $\sigma_c = \boldsymbol{c}^\top \boldsymbol{B}^{-1} \boldsymbol{M} \boldsymbol{B}^{-1}$.

Sample Size for an End-of-Study Comparison

Three timepoints, exchangeable correlation structure:

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

- $\delta = \mathrm{E}[Y_T^{(d)} - Y_T^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_T^{(d)}) + \mathrm{Var}(Y_T^{(d')})\right)/2}$ 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 $t \neq t'$

. Seewald, N. J., et al. (2019). *Statistical Methods in Medical Research*.

Sample Size for an End-of-Study Comparison

Three timepoints, exchangeable correlation structure:

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

- $\delta = \mathrm{E}[Y_T^{(d)} - Y_T^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_T^{(d)}) + \mathrm{Var}(Y_T^{(d')})\right)/2}$ 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 $t \neq t'$

. Seewald, N. J., et al. (2019). *Statistical Methods in Medical Research*.

Sample Size for an End-of-Study Comparison

Three timepoints, exchangeable correlation structure:

$$N \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2} \cdot \underbrace{(1-\rho^2)}_{\text{Deflation: longitudinal outcome}} \cdot \left(2 - P(R_i = 1)\right)$$

- $\delta = \mathrm{E}[Y_T^{(d)} - Y_T^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_T^{(d)}) + \mathrm{Var}(Y_T^{(d')})\right)/2}$ 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 $t \neq t'$

. Seewald, N. J., et al. (2019). *Statistical Methods in Medical Research*.

Sample Size for an End-of-Study Comparison

Three timepoints, exchangeable correlation structure:

$$N \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2} \cdot (1-\rho^2) \cdot \underbrace{\left(2 - P(R_i = 1)\right)}_{\text{Inflation: SMART design}}$$

- $\delta = \mathrm{E}[Y_T^{(d)} - Y_T^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_T^{(d)}) + \mathrm{Var}(Y_T^{(d')})\right)/2}$ 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 $t \neq t'$

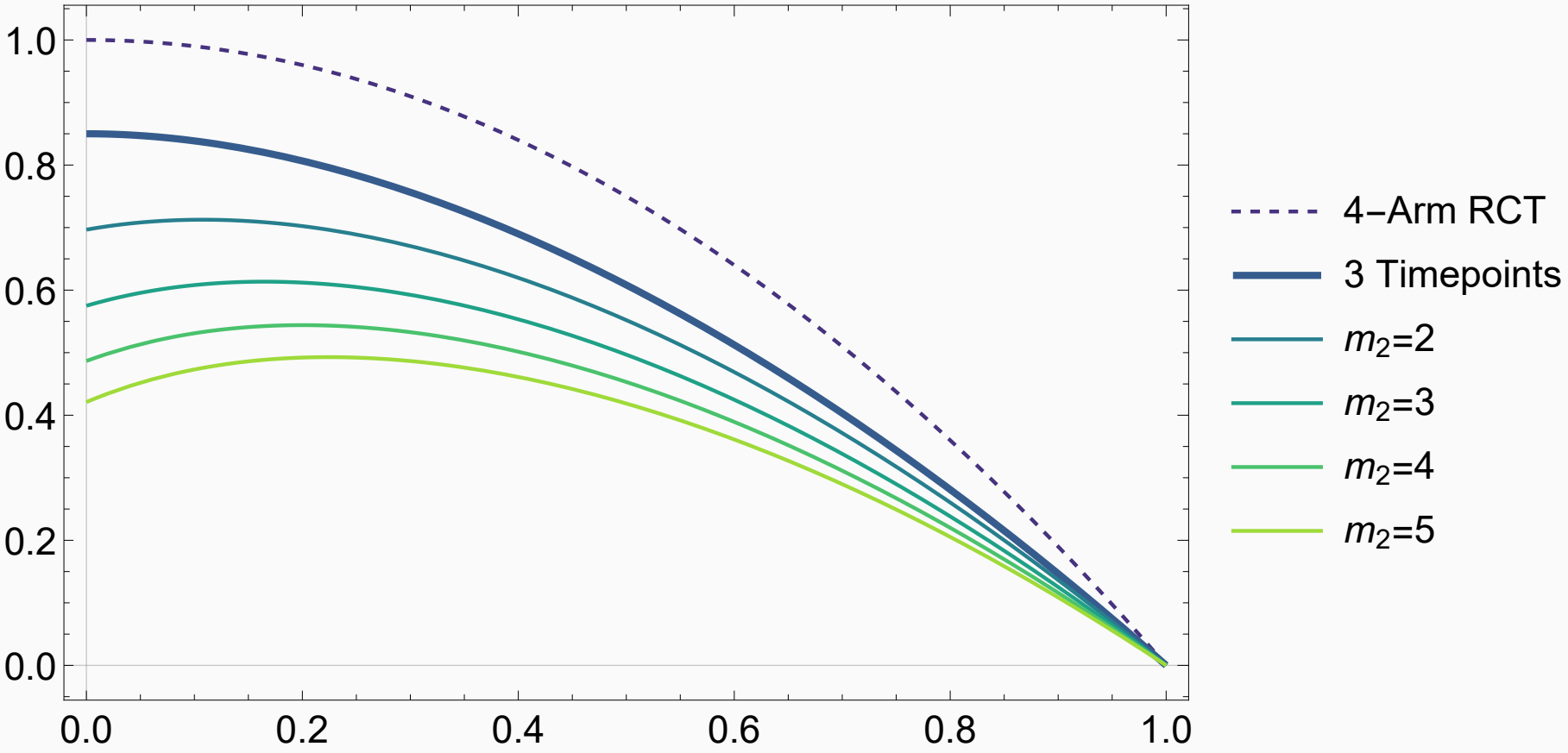
. Seewald, N. J., et al. (2019). *Statistical Methods in Medical Research*.

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

Preliminary Results for Adding Timepoints in Stage 2



Sample size multiplier vs. Exchangeable ρ, assuming P(R=1)=0.3. m_2 is num. timepoints after second randomization.

Extension to More than Three Timepoints

- A work in progress!
- Challenges:
  - When should we add timepoints? First stage? Second stage? Both?
  - Working assumptions needed for partial ordering on variance matrices
  - Intuition behind non-monotone relationship between sample size and ρ

Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research
0(0) 1–22

DOI: 10.1177/0962280219877520
journals.sagepub.com/home/smm
SAGE

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

Nicholas J Seewald,[1] Kelley M Kidwell,[2] Inbal Nahum-Shani,[3] Tianshuang Wu,[4] James R McKay[5] and Daniel Almirall[1,3]

arXiv:1810.13094 [stat.ME]

Funding

This work was supported by the National Institutes of Health (R01HD073975, U54EB020404, R03MH097954, R01MH114203, P01AA016821, RC1AA019092, R01DA039901, P50DA039838, R01DA047279, U01CA229437) and the Institute of Education Sciences (R324B180003).The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

https:\\nickseewald.com