Sample size and timepoint tradeoffs for comparing dynamic treatment regimens in a longitudinal SMART

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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*.

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

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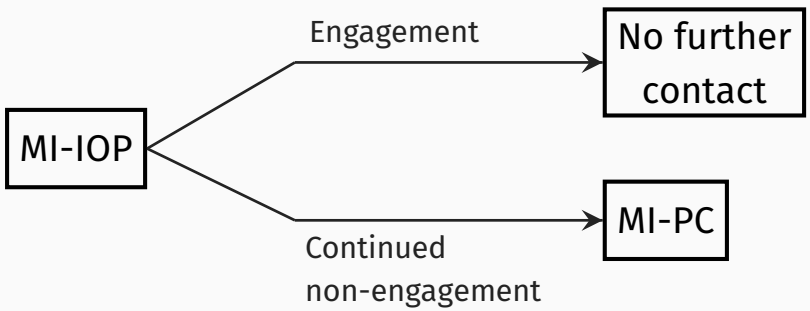
Dynamic Treatment Regimens

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 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.

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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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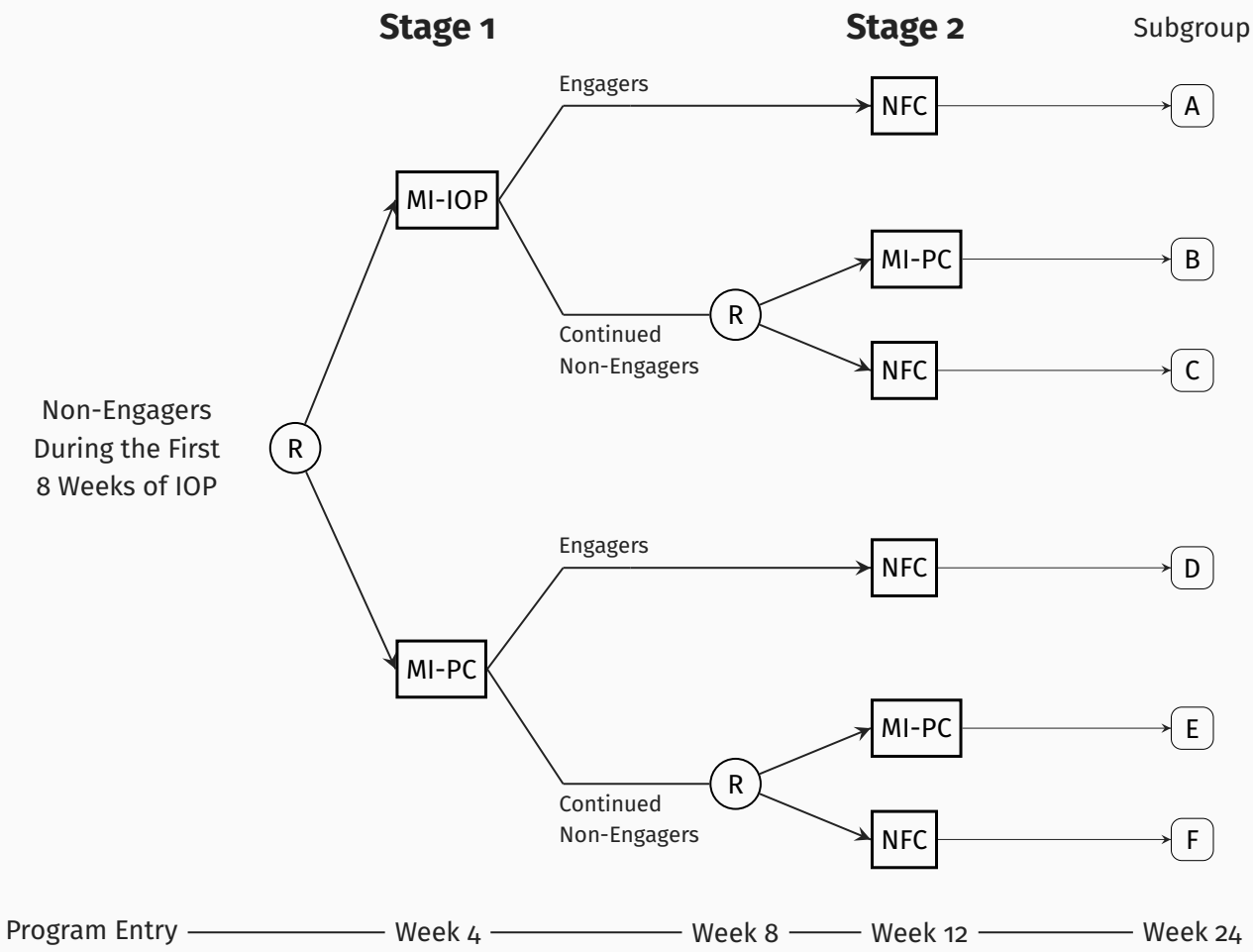

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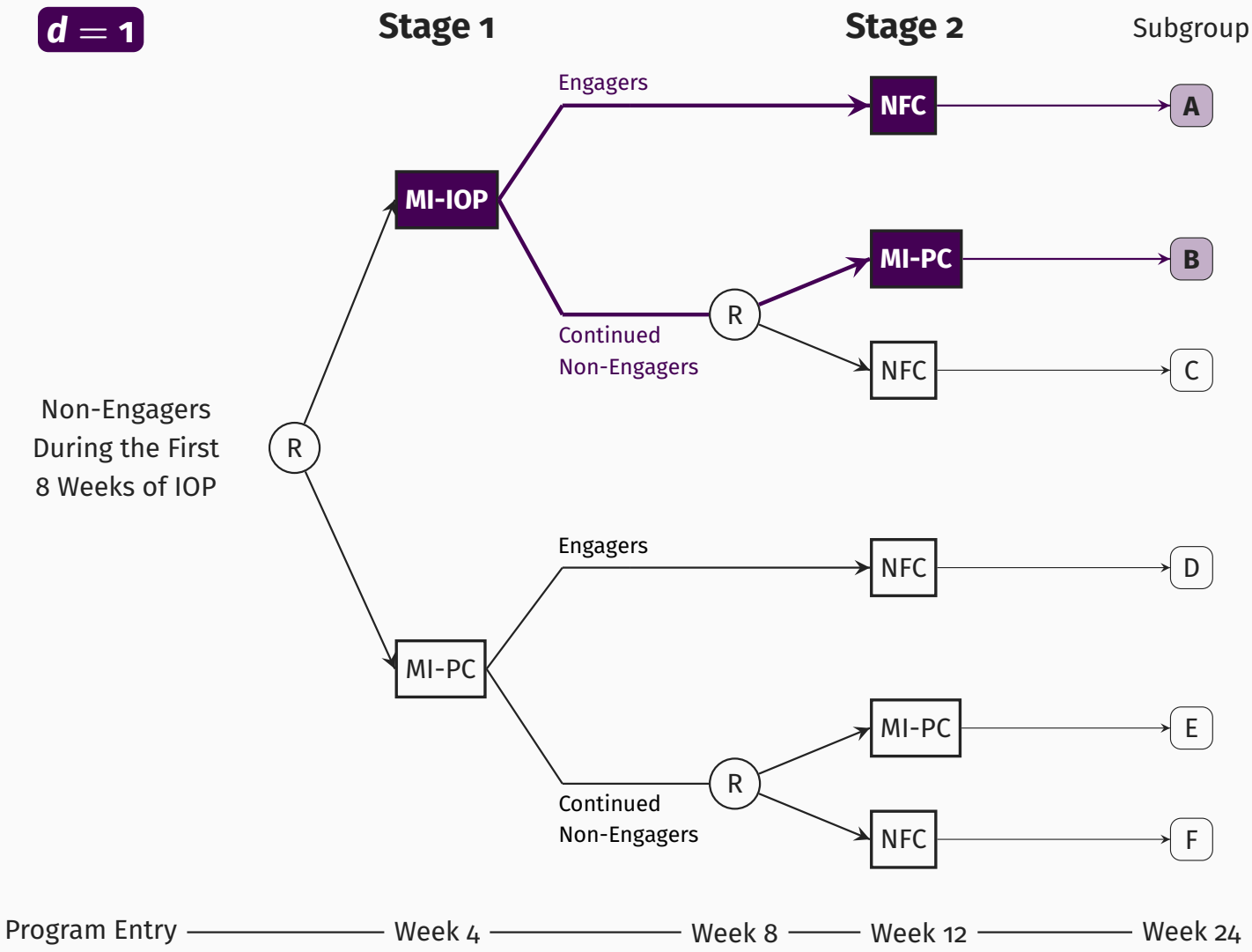
Four Embedded DTRs in ENGAGE



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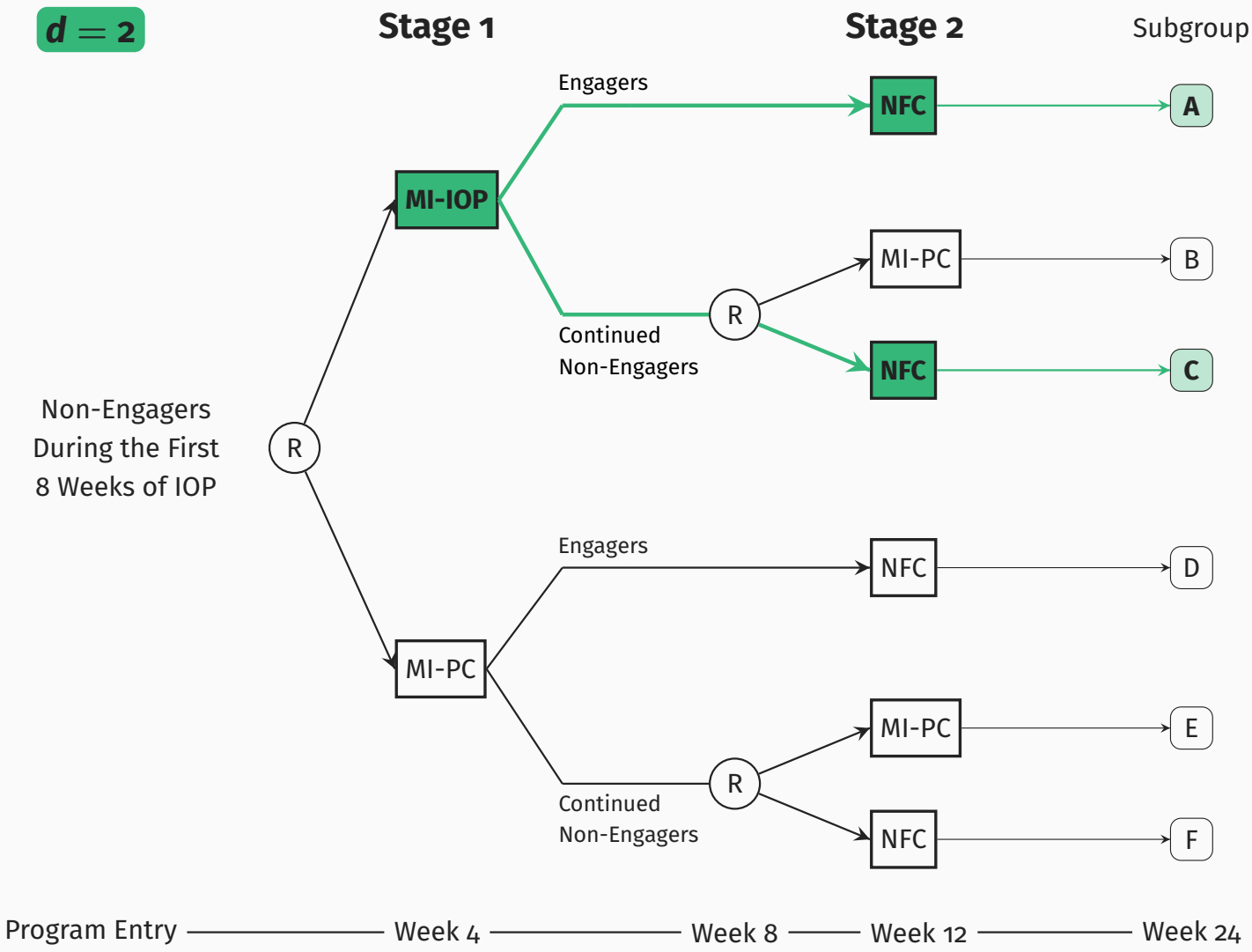

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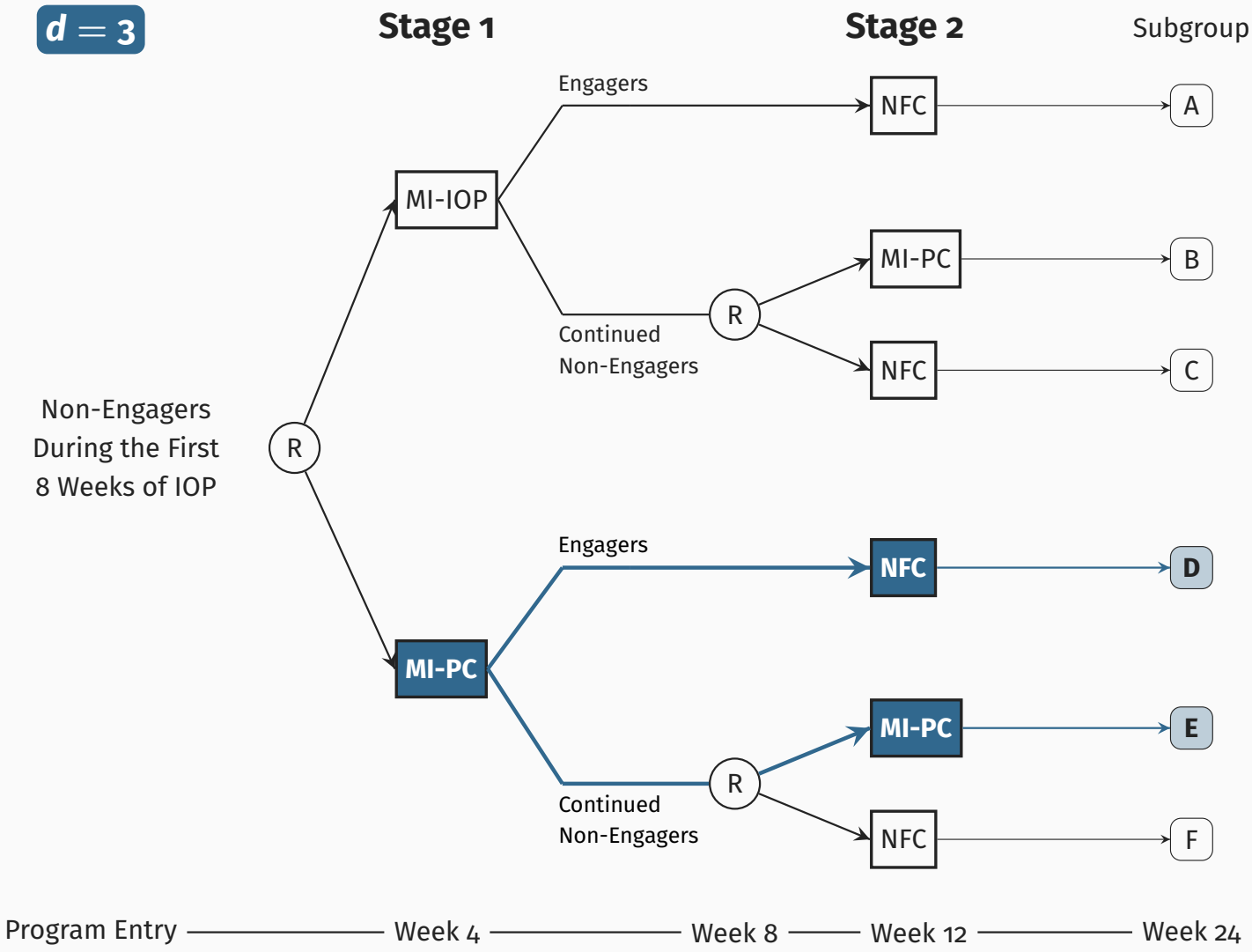

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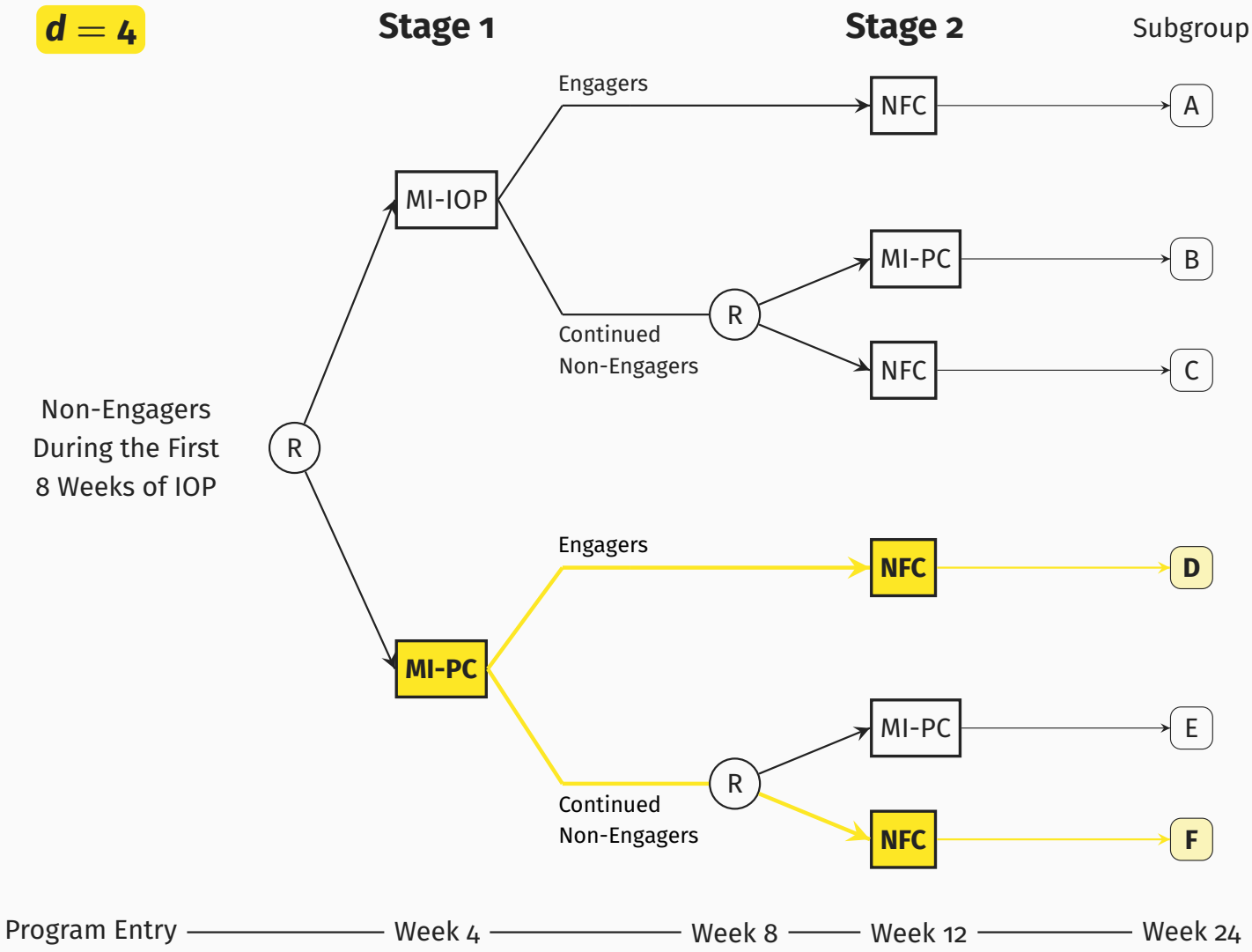
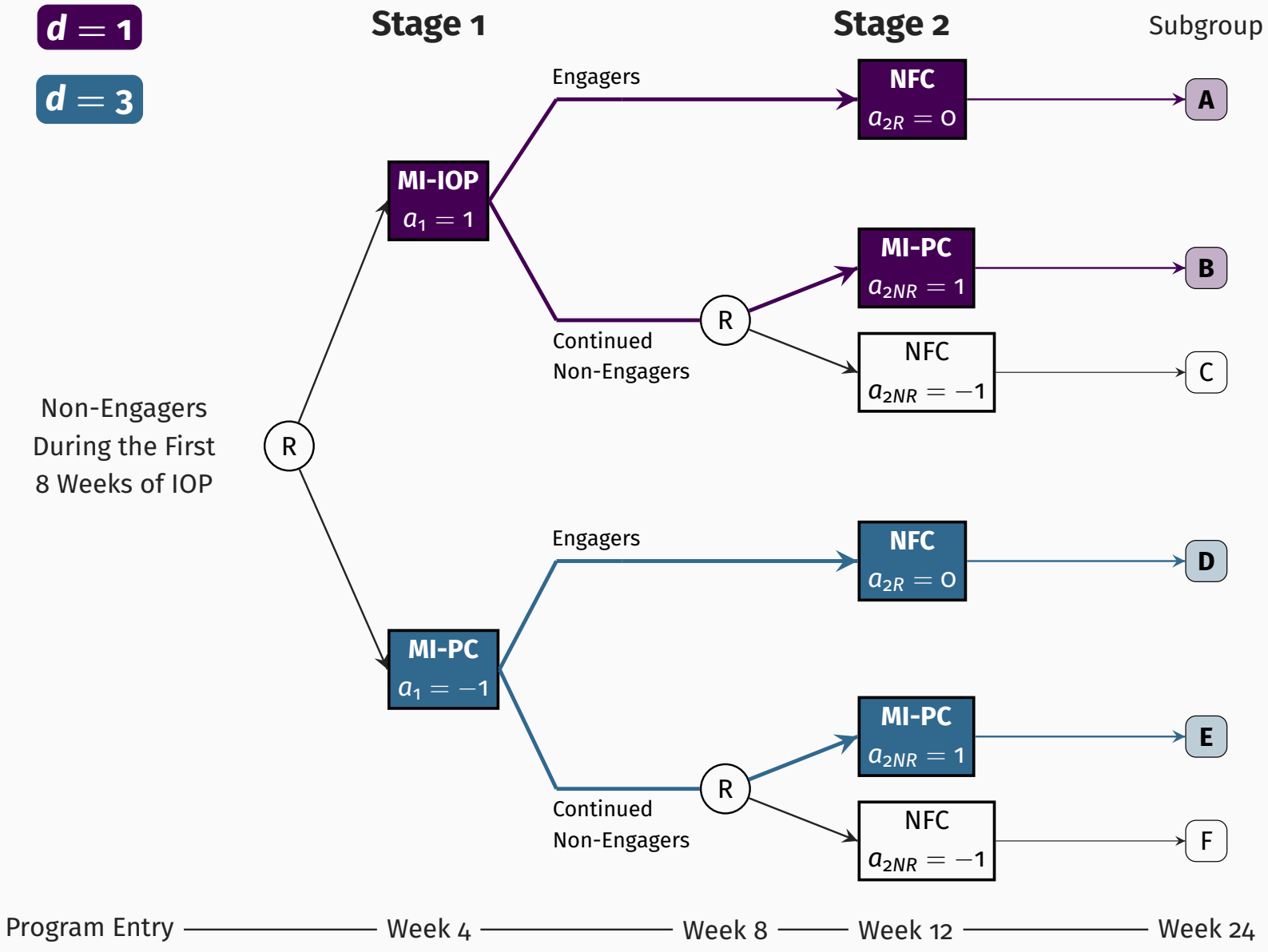
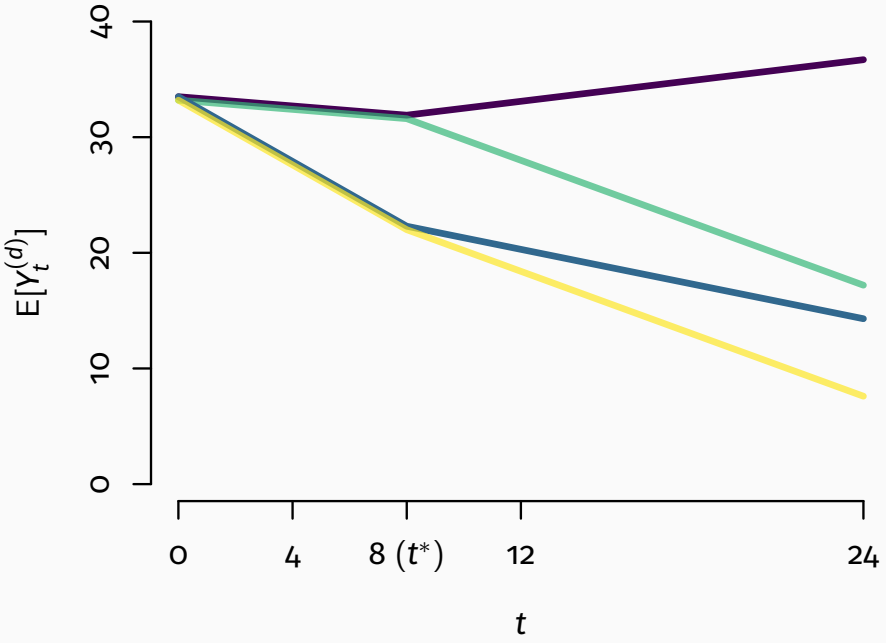


Common Primary Aim: Compare Embedded DTRs at End of Study



Our goal
is to develop a sample size formula for the comparison of two embedded DTRs at the end of the study using a longitudinal outcome collected at an arbitrary number of timepoints.

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 $\mathbf{Var}\left(\boldsymbol{Y}^{(d)} - \boldsymbol{\mu}^{(d)}(\beta) \right)$

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Goal

Goal: Develop a tractable sample size formula for the test

$$H_0 : \mathrm{E}\left[Y_T^{(d=1)} - Y_T^{(d=3)}\right] = 0 \quad \text{vs.} \quad H_1 : \mathrm{E}\left[Y_T^{(d=1)} - Y_T^{(d=3)}\right] = \Delta.$$

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Under our example model,

$$\mathrm{E}\left[Y_T^{(d=1)} - Y_T^{(d=3)}\right] = \boldsymbol{c}^\top \boldsymbol{\beta}$$

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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 $\sigma_c = \boldsymbol{c}^\top \mathbf{Var}\left(\hat{\beta}\right) \boldsymbol{c}$.

Sample Size for an End-of-Study Comparison

Under mild working assumptions, exchangeable within-person correlation, and constant variance across time and DTRs:

$$N \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2} \cdot \left(2 - P(R_i = 1)\right) \cdot f(\rho, T_2, T)$$

- $\delta = \Delta/\sigma = \mathrm{E}[Y_T^{(d)} - Y_T^{(d')}] / \sqrt{\left(\mathrm{Var}(Y_T^{(d)}) + \mathrm{Var}(Y_T^{(d')})\right)/2}$ is the target standardized effect size
- α is the desired type-I error
- $1 - \gamma$ is the desired power
- $\rho = \mathrm{cor}(Y_t, Y_{t'})$ for $t \neq t'$
- T is the total number of measurement occasions
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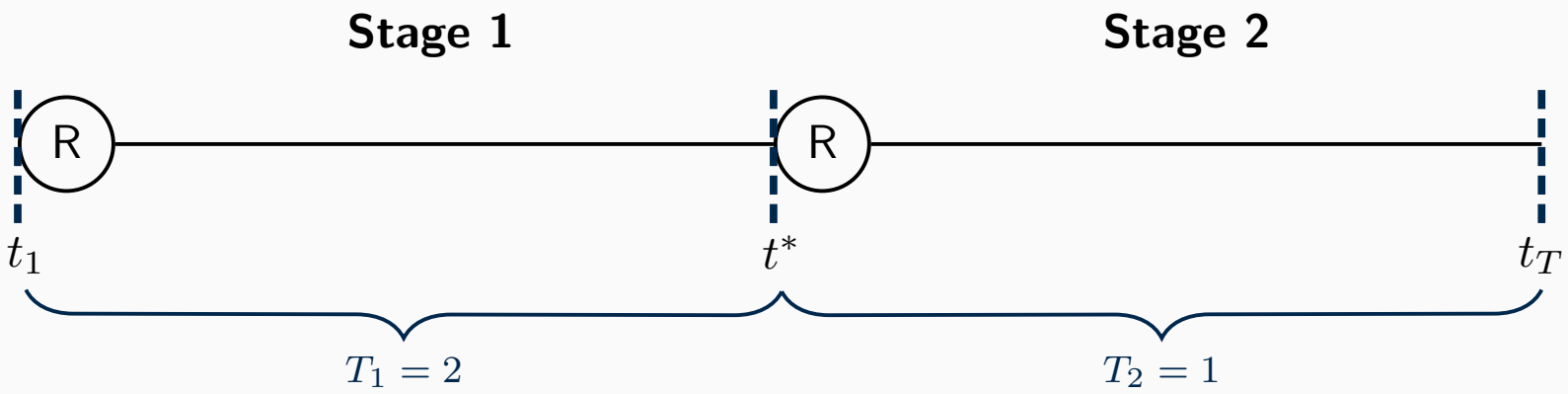
Long-Term Goal: Understand tradeoffs between N, T_2, and T to maximize power subject to a budget constraint.

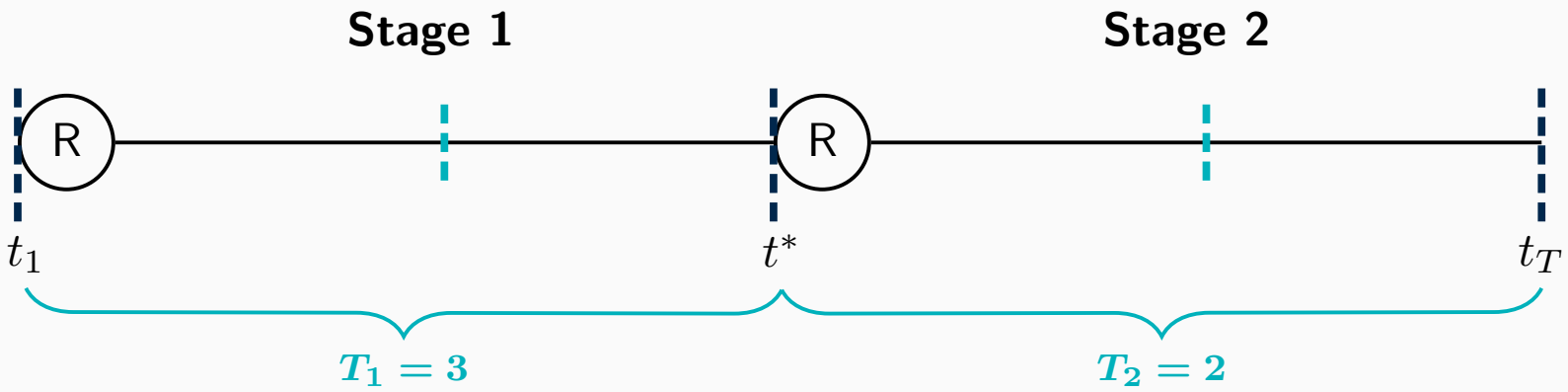
Special Case: 3 timepoints simplifies nicely



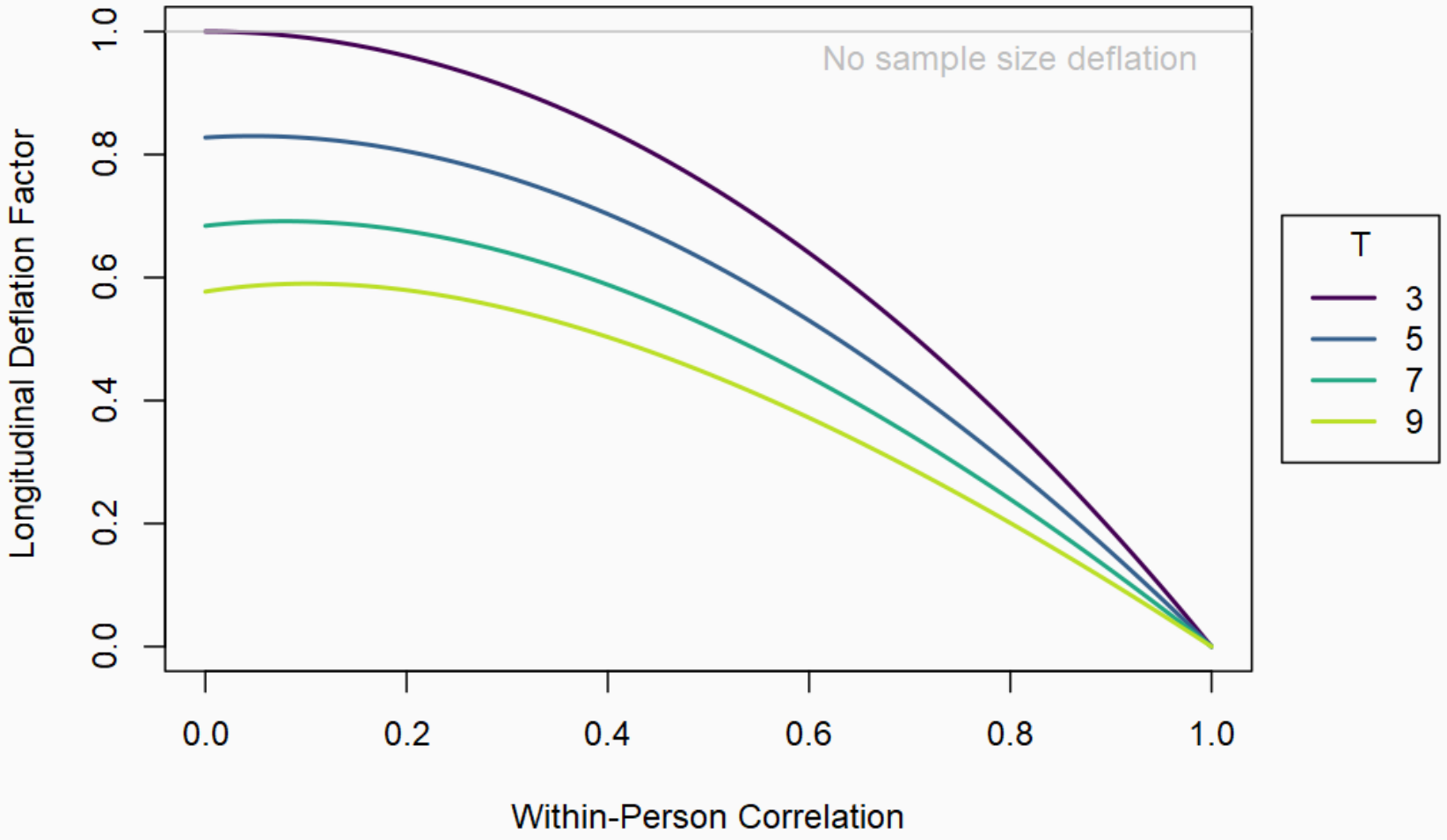
$$f(\rho, 1, 3) = (1 - \rho^2)$$

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

One strategy is to add timepoints in both stages of the SMART

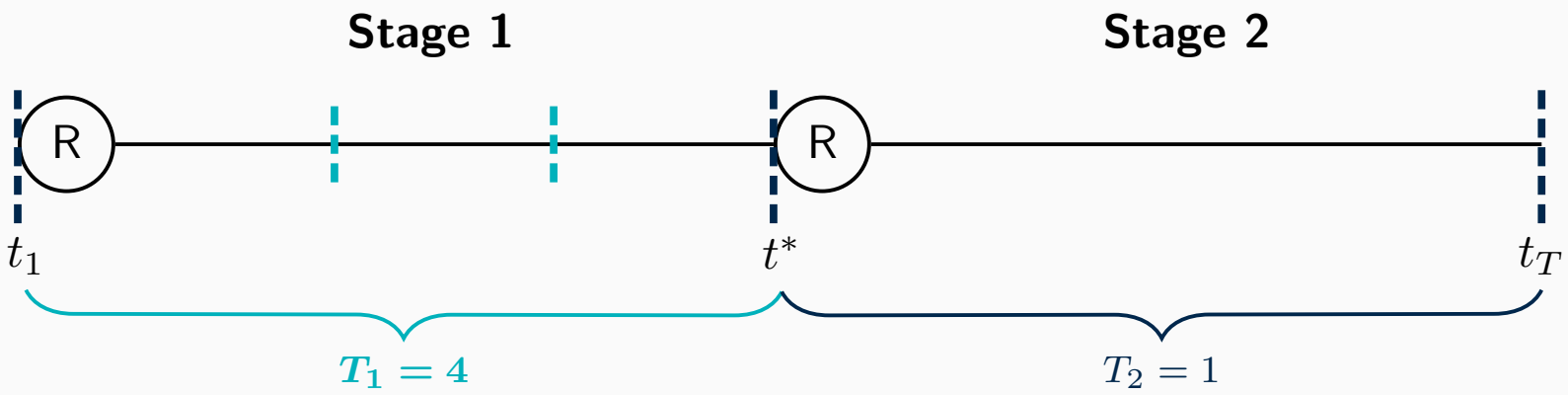


Understanding $f(\rho, T_2, T)$: Increase T, fix $T_2 = \lfloor T/2 \rfloor$



Increasing T increases power.

Do we benefit from unequal distribution of timepoints?



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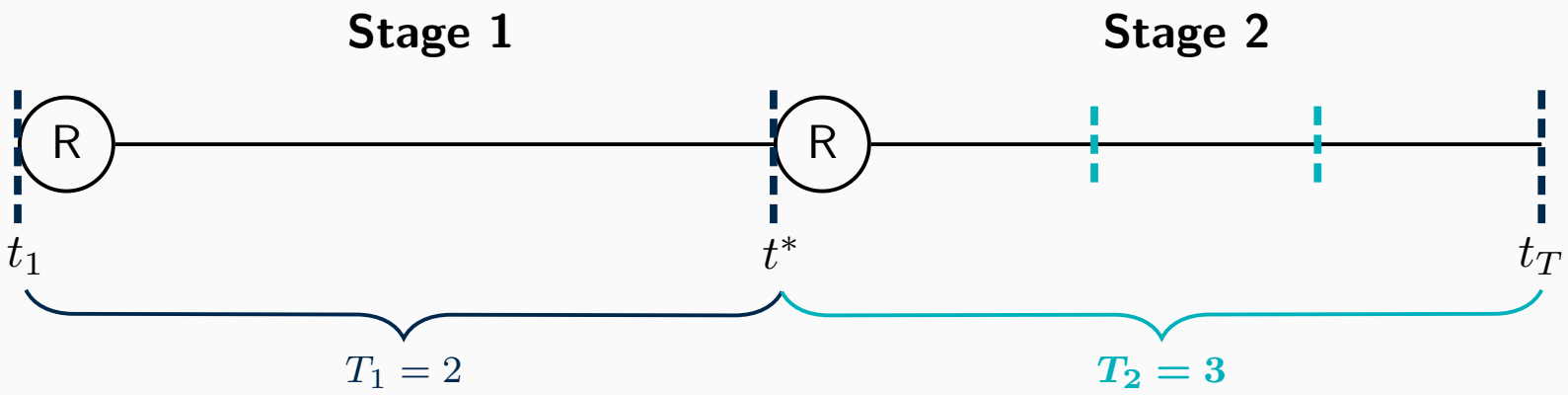
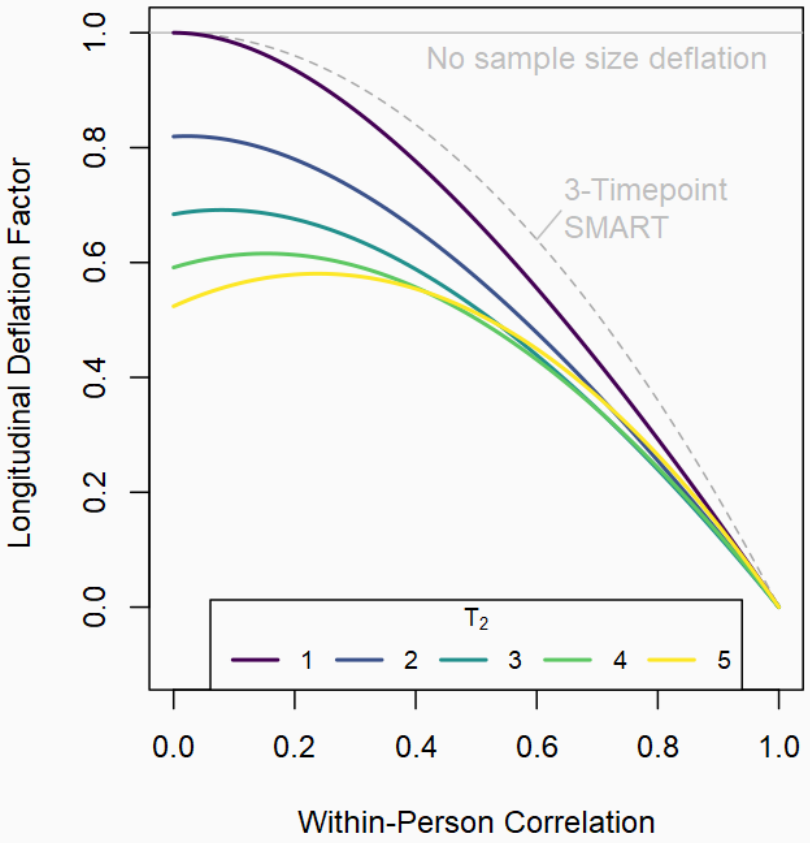
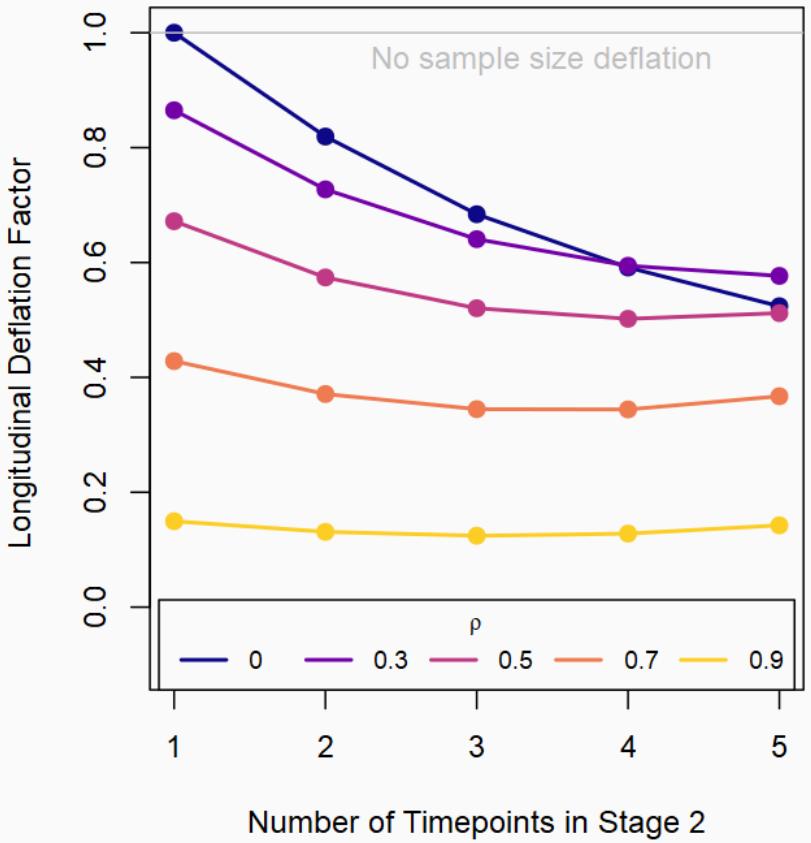


Understanding $f(\rho, T_2, T)$: Fix $T = 7$, increase T_2





$f(\rho, T_2, T)$ becomes non-monotone in ρ as T_2 increases; adding measurements matters less as ρ increases.

Coming Soon

- A work in progress!
- Still to Come:
  - User-friendly sample size tool: $f(\rho, T_2, T)$ is somewhat complex
  - Guidance on balancing N and T subject to a budget constraint
  - Intuition behind non-monotone relationship between sample size and ρ

Article

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

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