Design and Analytic Considerations for Sequential, Multiple-Assignment Randomized Trials with Longitudinal Outcomes

Oral Defense

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Materials Available Online

nickseewald.com/talk/defense

"Ignorance of whether or how to change psychotherapies is a major and persisting gap in psychiatric knowledge."

J. C. Markowitz and B. L. Milrod. "What to Do When a Psychotherapy Fails". In: *The Lancet Psychiatry* 2.2 (2015), pp. 186–190

Dynamic Treatment Regimens

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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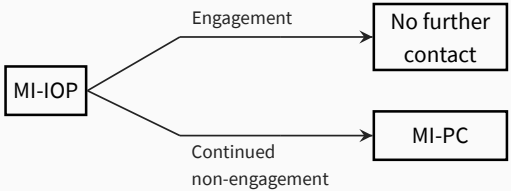
Dynamic Treatment Regimens

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.

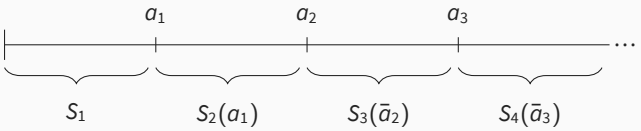
Chakraborty, B. and Moodie, E. E. M. (2013). *Statistical Methods for Dynamic Treatment Regimes*.

Dynamic Treatment Regimens

Suppose we want to recommend a sequence of M treatments, $a_1, \ldots, a_M$.

Define $\bar{a}_j = \{a_1, \ldots, a_j\}$

$S_j(\bar{a}_{j-1})$ is collected after providing treatment a_{j-1} until just before providing a_j.



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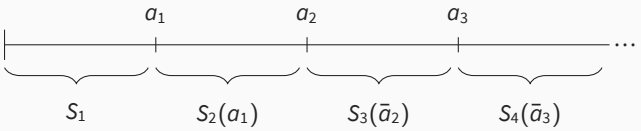

Define $\bar{S}_j(\bar{a}_{j-1}) = \{S_1, S_2(a_1), \ldots, S_j(\bar{a}_{j-1})\}$

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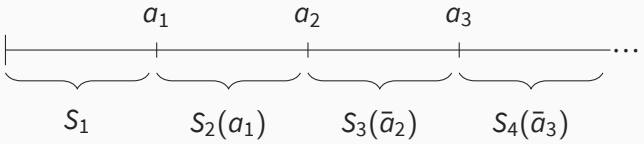
Dynamic Treatment Regimens



Definition
A **decision rule** φ_j is a function of $\bar{S}_j(\bar{a}_{j-1})$ which outputs a recommendation for subsequent treatment a_j.

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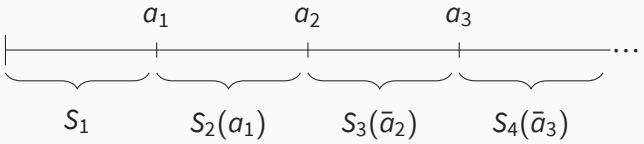
Dynamic Treatment Regimens

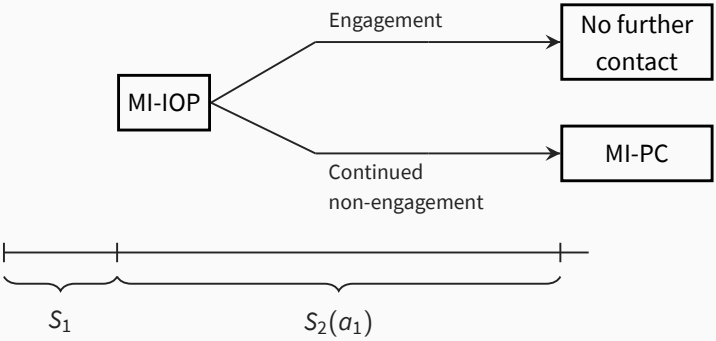


Definition
A **decision rule** φ_j is a function of $\bar{S}_j(\bar{a}_{j-1})$ which outputs a recommendation for subsequent treatment a_j.

Definition
An ***M*-stage dynamic treatment regimen** is a sequence of M decision rules $\{\varphi_1, \ldots, \varphi_M\}$

Murphy, S. A. (2005). *Statistics in Medicine*.

An Example Two-Stage DTR



Tailoring Variables

Often, $S_j(\bar{a}_{j-1})$ contains information used to inform the recommendation to subsequent treatment.

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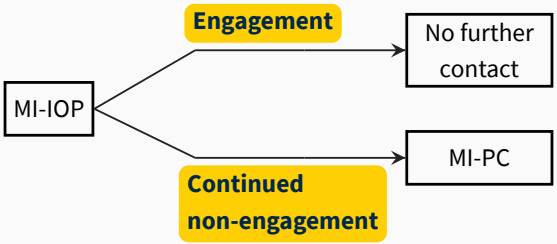
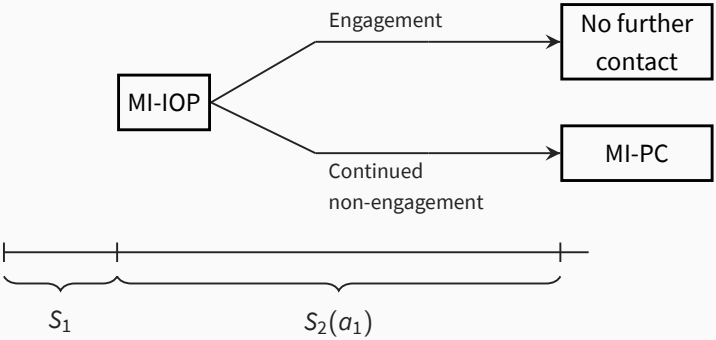


$R(a_1) \in S_2(a_1)$

$R(a_1) = \mathbb{1}\{\text{Individual did not fail to attend two or more IOP sessions in one week}\}$

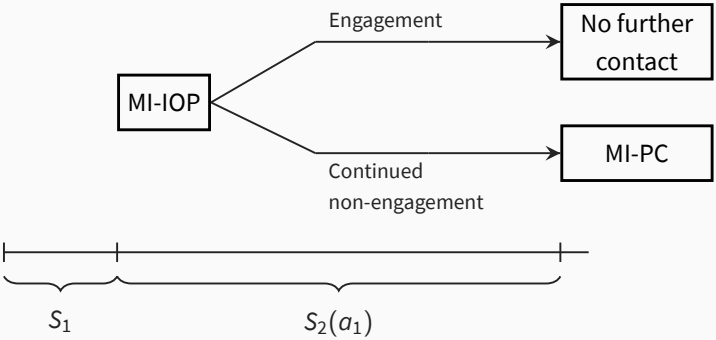
An Example Two-Stage DTR



This DTR can be written $\{\varphi_1, \varphi_2\}$, where

$$\varphi_1(S_1) = \text{MI-IOP}$$
$$\varphi_2\left(\bar{S}_2(a_1)\right) = R \cdot (\text{No further contact}) + (1 - R) \cdot (\text{MI-PC})$$

An Example Two-Stage DTR



More intuitively, for 2-stage DTRs, we can write $\{\varphi_1, \varphi_2\}$ as

$$(a_1, a_{2R}, a_{2NR}) = (\text{MI-IOP, NFC, MI-PC})$$

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.

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?

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Scientific Questions about DTRs

- Which is the more effective first-stage intervention option?
- Which is the more effective second-stage intervention option for responders?
- Which is the more effective second-stage intervention option for non-responders?
- Which of two DTRs is more effective overall?
- Which of two tailoring variables leads to better overall outcomes?
- etc.

Sequential, Multiple-Assignment Randomized Trials

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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.

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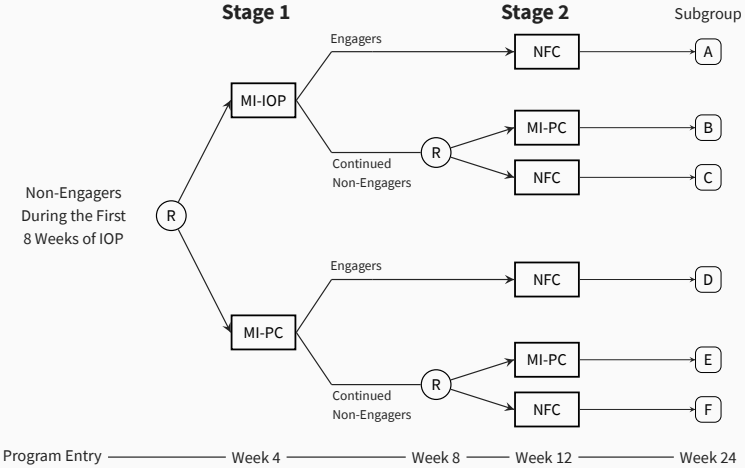
The key feature of a SMART is that some (or all) participants are randomized *more than once*.

Motivating Example: The ENGAGE Study



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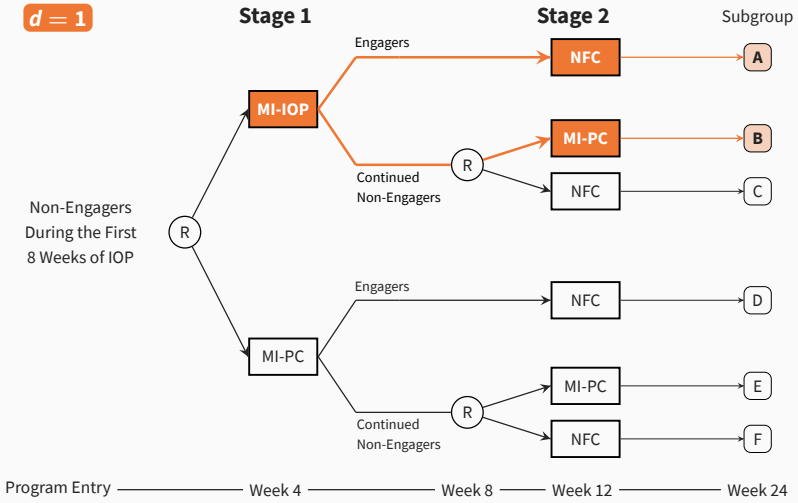
Four Embedded DTRs in ENGAGE



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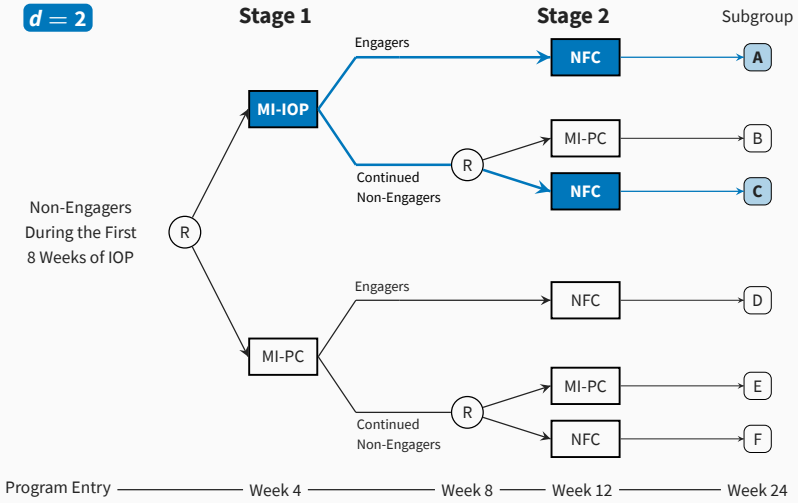

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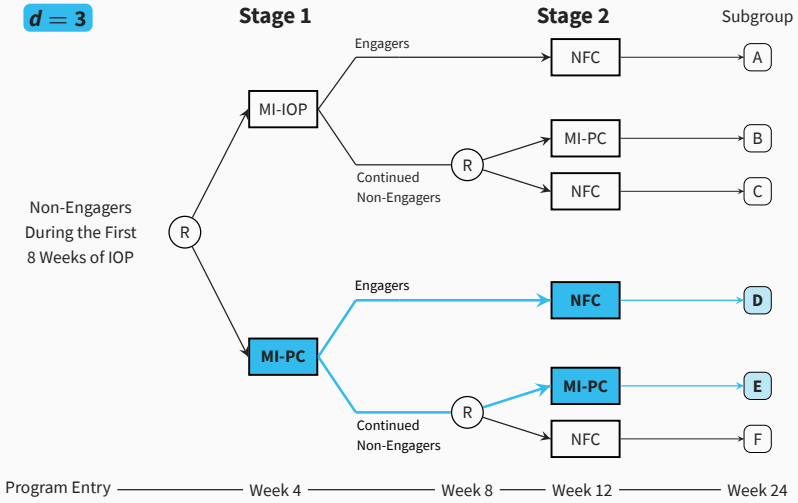

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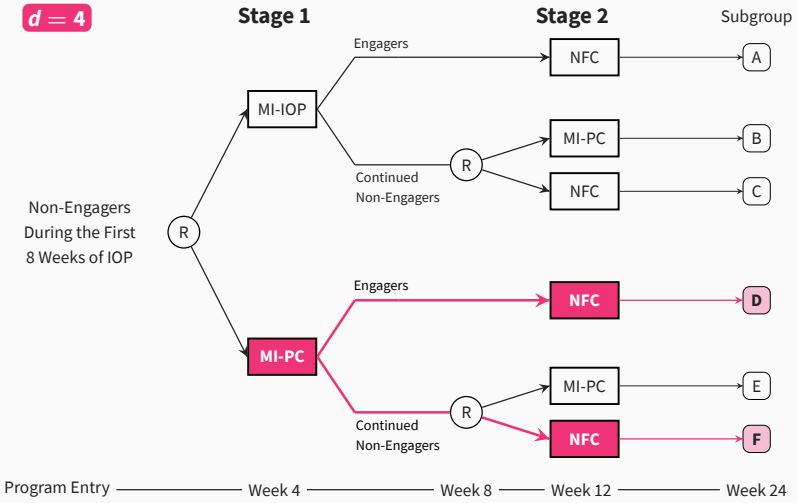
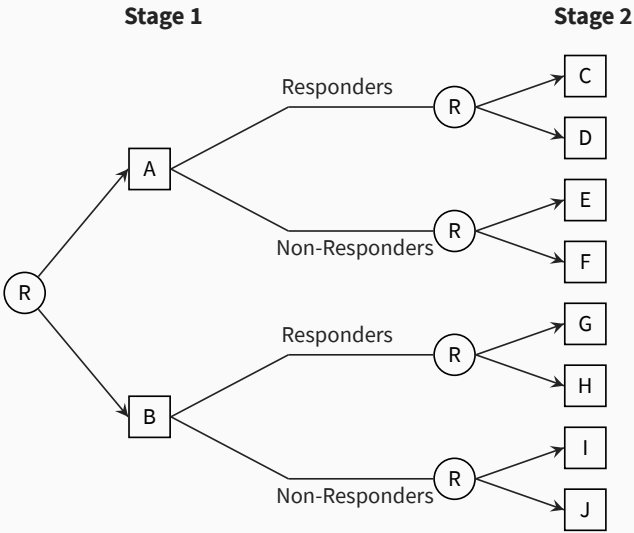


Other SMART Designs



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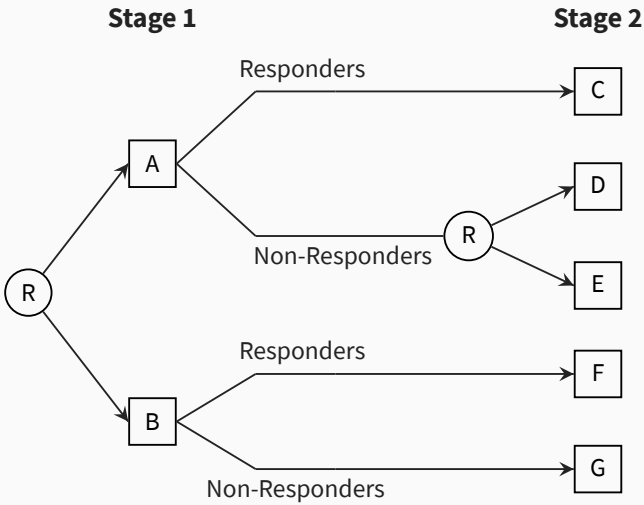
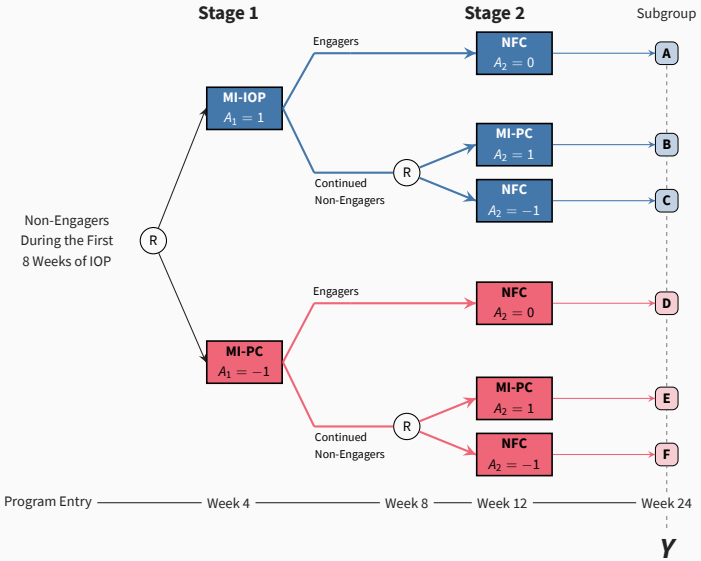
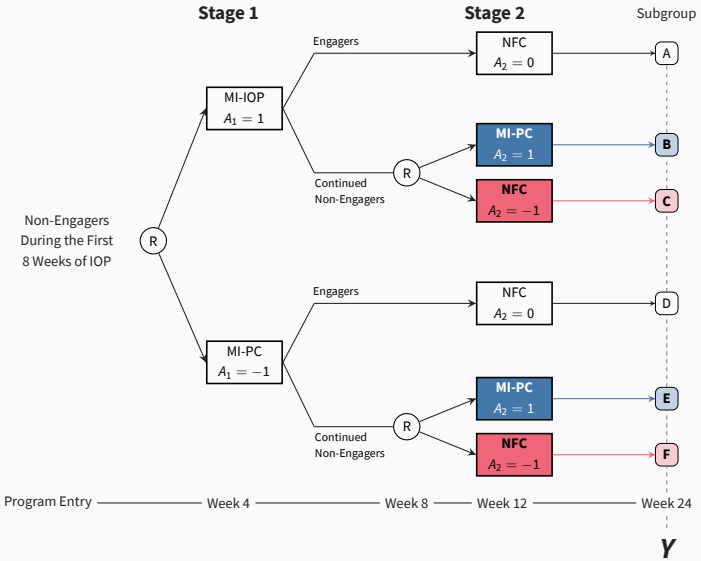


Common Primary Aim: Compare First-Stage Treatments in Context of a DTR



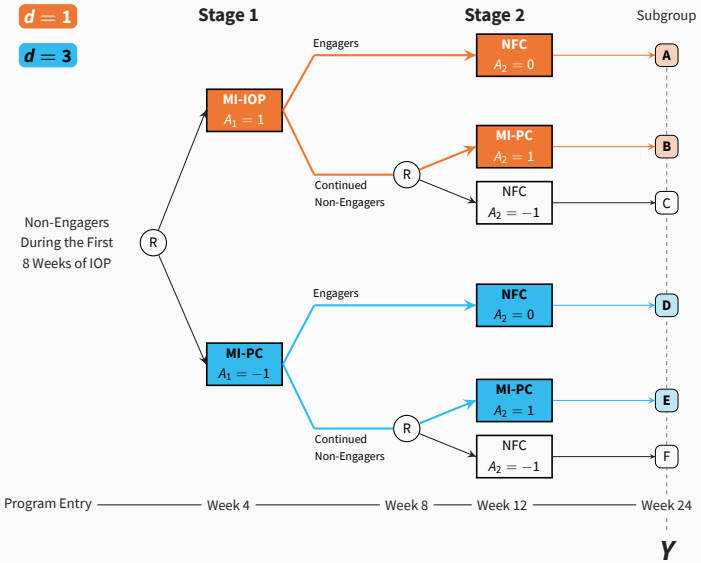
$$\mathop{\mathrm{E}}_{R,A_2,Y}\left[Y^{(1,\cdot,\cdot)} - Y^{(-1,\cdot,\cdot)}\right]$$

Common Primary Aim: Compare Second-Stage Treatments among Non-Responders



$$\mathop{\mathbb{E}}_{A_1,Y}\left[Y^{(\cdot,\cdot,1)} - Y^{(\cdot,\cdot,-1)} \mid R = 0\right]$$

Common Primary Aim: Compare Embedded DTRs at End of Study



$$\underset{R,Y}{\mathrm{E}}\left[Y^{(1,0,1)} - Y^{(-1,0,1)}\right]$$

Common Primary Aim: Compare Embedded DTRs at End of Study

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

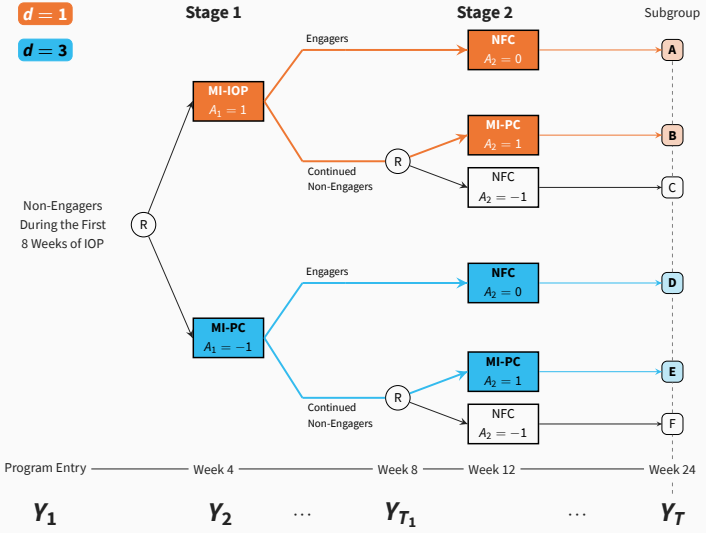
Common Primary Aim: Compare Embedded DTRs at End of Study

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

Methods exist for comparing embedded DTRs using

- **Continuous outcomes:** S. A. Murphy (2005). *Statistics in Medicine*
  A. I. Oetting et al. (2011). *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures*
  I. Nahum-Shani et al. (2012). *Psychological Methods*
  S. B. Ogbagaber, J. Karp, and A. S. Wahed (2016). *Statistics in Medicine*
- **Survival outcomes:** W. Feng and A. S. Wahed (2009). *Statistics in Medicine*
  Z. Li and S. A. Murphy (2011). *Biometrika*
  K. M. Kidwell and A. S. Wahed (2013). *Biostatistics*
- **Binary outcomes:** K.M. Kidwell, N.J. Seewald, et al. (2018). *Journal of Applied Statistics*
- **Clustered outcomes:** T. NeCamp, A. Kilbourne, and D. Almirall (2017). *Statistical Methods in Medical Research*

Our Contribution



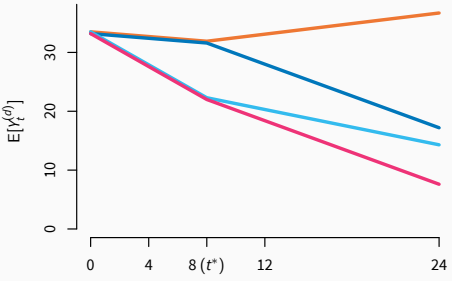
Our Contribution

Develop sample size methods for SMARTs with continuous longitudinal outcomes in which the primary aim is end-of-study comparison of two embedded DTRs which recommend different first-stage treatments.

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

Modeling Continuous Longitudinal Outcomes in SMARTs

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

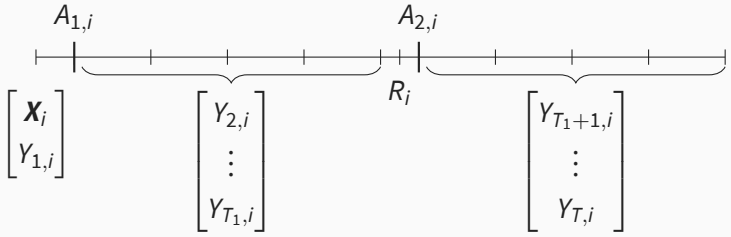
$$
\begin{aligned}
\mathrm{E}\left[Y_t^{(d)} \mid \boldsymbol{X}\right] &:= \mu_t^{(d)}(\boldsymbol{\eta}, \boldsymbol{\beta}) \\
&= \boldsymbol{\eta}^\top \boldsymbol{X}_i + \beta_0 \\
&\quad + \mathbb{1}\{t \le t^*\}\{\beta_1 t + \beta_2 a_1 t\} \\
&\quad + \mathbb{1}\{t > t^*\}\{t^*\beta_1 + t^*\beta_2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

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

Observed Data

For the ith individual, we collect

$$\left(\boldsymbol{X}_i, Y_{1,i}, A_{1,i}, \boldsymbol{Y}_{2:T_1,i}, R_i, A_{2,i}, \boldsymbol{Y}_{T_1+1:T,i}\right)$$



M-Estimation of Model Parameters

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

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

M-Estimation of Model Parameters

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- d specifies an embedded DTR

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

M-Estimation of Model Parameters

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

- $\boldsymbol{V}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\tau})$ is a working model for $\mathbf{Var}\left(\boldsymbol{Y}^{(d)} - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta}) \right)$
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Lu, X. et al. (2016). *Statistics in Medicine*.

M-Estimation of Model Parameters

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$$\left. \cdot \underbrace{\left(\boldsymbol{D}^{(d)}(\boldsymbol{X}_i) \right)^{\top}}_{\text{Jacobian of } \mu^{(d)}} \cdot \boldsymbol{V}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\tau})^{-1} \cdot \left(\boldsymbol{Y}_i - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta}) \right) \right],$$

- $\boldsymbol{D}^{(d)}(\boldsymbol{X}_i) = \frac{\partial}{\partial (\boldsymbol{\eta}^{\top}, \boldsymbol{\beta}^{\top})^{\top}} \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta})$
- $\boldsymbol{V}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\tau})$ is a working model for $\mathbf{Var}\left(\boldsymbol{Y}^{(d)} - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta}) \right)$
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M-Estimation of Model Parameters

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

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

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

M-Estimation of Model Parameters

$$0 = \sum_{i=1}^{N} \underbrace{\sum_{d}}_{\text{Sum over DTRs}} \left[\frac{I^{(d)}(A_{1,i}, R_i, A_{2,i})}{P(A_{1,i} = a_1) P(A_{2,i} = a_2 \mid A_{1,i} = a_1, R_i)} \right.$$

$$\left. \cdot \left(\boldsymbol{D}^{(d)}(\boldsymbol{X}_i) \right)^{\top} \cdot \boldsymbol{V}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\tau})^{-1} \cdot \left(\boldsymbol{Y}_i - \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta}) \right) \right],$$

- $I^{(d)}(A_{1,i}, R_i, A_{2,i}) = \mathbb{1}\{A_{1,i} = a_1\} \left(R_i + (1 - R_i)\, \mathbb{1}\{A_{2,i} = a_2\} \right)$ for ENGAGE
- $\boldsymbol{D}^{(d)}(\boldsymbol{X}_i) = \frac{\partial}{\partial (\boldsymbol{\eta}^{\top}, \boldsymbol{\beta}^{\top})^{\top}} \boldsymbol{\mu}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\eta}, \boldsymbol{\beta})$
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- d specifies an embedded DTR

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

Iterated Estimation Procedure

Let $\boldsymbol{\theta} = (\boldsymbol{\eta}^\top, \boldsymbol{\gamma}^\top)^\top$ be the vector of parameters in the marginal model.

1. Solve the estimating equations using $\boldsymbol{V}^{(d)}(\boldsymbol{X}_i; \boldsymbol{\tau}) = \boldsymbol{I}_{T\times T}$, call the solution $\hat{\boldsymbol{\theta}}_{(0)}$.
2. Use $\hat{\boldsymbol{\theta}}_{(0)}$ to estimate $\boldsymbol{\tau}$, call the estimate $\hat{\boldsymbol{\tau}}_{(0)}$.
3. Use $\hat{\boldsymbol{\tau}}_{(0)}$ in the estimating equations to get a new estimate for $\boldsymbol{\theta}$
4. Iterate until convergence.

Seewald, N. J. et al. (2020). *Stat Methods Med Res*.

Asymptotics

- Call the solution to the estimating equations $\hat{\boldsymbol{\theta}}$
- Under usual regularity conditions:
  - $\hat{\boldsymbol{\theta}} \xrightarrow{p} \boldsymbol{\theta}^*$
  - $\sqrt{n}\left(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}^*\right) \Rightarrow \mathcal{N}\left(\mathbf{0}, \boldsymbol{B}^{-1}\boldsymbol{M}\boldsymbol{B}^{-1}\right)$

where

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

$$\boldsymbol{M} := \mathsf{E}\left[\left(\sum_{d\in\mathcal{D}} W^{(d)}\left(A_1, R, A_2\right) \boldsymbol{D}^{(d)}(\boldsymbol{X})^\top \boldsymbol{V}^{(d)}(\boldsymbol{X};\boldsymbol{\tau})^{-1} \left(\boldsymbol{Y} - \boldsymbol{\mu}^{(d)}(\boldsymbol{X};\boldsymbol{\theta})\right)\right)^{\otimes 2}\right]$$

See, e.g., van der Vaart, A. W. (1998). *Asymptotic Statistics*, for details on regularity.

Sample Size for Comparing DTRs in Longitudinal SMARTs

Some Simplifications and Notation

- No baseline covariates (conservative)
- Measurement occasions are equally spaced in both stages
  - T_1 measurements in stage 1 (includes baseline)
  - T_2 measurements in stage 2
  - $T = T_1 + T_2$ total measurements

Goal

Goal: Develop a tractable sample size formula for the test

$$H_0 : \mathrm{E}\left[Y_T^{(1,a_{2R},a_{2NR})} - Y_T^{(-1,a'_{2R},a'_{2NR})}\right] = 0 \quad \text{vs.} \quad H_1 : \mathrm{E}\left[Y_T^{(1,a_{2R},a_{2NR})} - Y_T^{(-1,a'_{2R},a'_{2NR})}\right] = \Delta.$$

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Under our example model,

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

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Under our example model,

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So hypotheses become

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

A Test Statistic

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

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

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

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

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

Sample Size for an End-of-Study Comparison of DTRs

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

$$n \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2} \cdot \mathrm{DE}\left(\boldsymbol{r}\right) \cdot \omega(\rho, T, T_2)$$

- $\delta = \Delta/\sigma$ is the target standardized effect size
- α is the desired type-I error
- $1 - \gamma$ is the desired power
- $\boldsymbol{r} = (r_1, r_{-1})^\top$ is a vector of response probabilities
- $\rho = \mathrm{cor}(Y_t, Y_{t'})$ for $t \neq t'$
- T is the total number of measurements
- T_2 is the number of measurements in stage 2

Seewald, N. J. et al. (2020). *Stat Methods Med Res*.

Sample Size for an End-of-Study Comparison of DTRs

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

$$n \geq \underbrace{\frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2}}_{\text{Standard sample size for a 2-arm trial}} \cdot \mathrm{DE}(\boldsymbol{r}) \cdot \omega(\rho, T, T_2)$$

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Sample Size for an End-of-Study Comparison of DTRs

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Why deflation?

- Correlation is *within-person*, but analysis is *between-DTRs*
- Within-person correlation yields more precise estimates of between-DTR differences

Seewald, N. J. et al. (2020). *Stat Methods Med Res*; Hedeker, D., Gibbons, R. D., and Waternaux, C. (1999). *J. Educ. Behav. Stat.*

Getting to a Sample Size Formula

Starting from the test statistic

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

$$\gamma = P\left(\left|\frac{\sqrt{n}\boldsymbol{c}^\top \hat{\boldsymbol{\theta}}}{\sigma_c}\right| \leq z_{1-\alpha/2} \mid \boldsymbol{c}^\top \boldsymbol{\theta} = \Delta\right)$$

$$\ddots$$

$$n \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\Delta^2} \cdot \sigma_c^2$$

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Challenge: Find a simple upper bound on σ_c^2 that yields an interpretable, tractable sample size formula.

Getting to a Sample Size Formula

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$$\sigma_c^2 = \boldsymbol{c}^\top \boldsymbol{B}^{-1} \boldsymbol{M} \boldsymbol{B}^{-1} \boldsymbol{c}$$

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

Working with $\boldsymbol{M}$ is challenging

Working Assumptions for Sample Size Formula

1. *Constrained conditional variability:*
   1.1 For all embedded DTRs d,

$$\mathrm{E}\left[\left(\boldsymbol{Y}_i^{(d)} - \boldsymbol{\mu}^{(d)}\right)^{\otimes 2} \mid R_i^{(d)} = 1\right] - \mathrm{E}\left[\left(\boldsymbol{Y}_i^{(d)} - \boldsymbol{\mu}^{(d)}\right)^{\otimes 2}\right]$$

   is positive semi-definite.

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   is positive semi-definite.

   1.2 For all embedded DTRs d,

$$\frac{1}{P\left(R_i^{(d)} = 1\right)} \mathrm{E}\left[\left(\boldsymbol{Y}_i^{(d)} - \boldsymbol{\mu}^{(d)}\right)^{\otimes 2}\right] - \mathrm{E}\left[\left(\boldsymbol{Y}_i^{(d)} - \boldsymbol{\mu}^{(d)}\right)^{\otimes 2} \mid R_i^{(d)} = 1\right]$$

   is positive semi-definite.

Working Assumptions for Sample Size Formula

2. *Constrained Conditional Means.* For every embedded DTR d and and all embedded DTRs d' such that $a_1^{(d)} \neq a_1^{(d')}$,

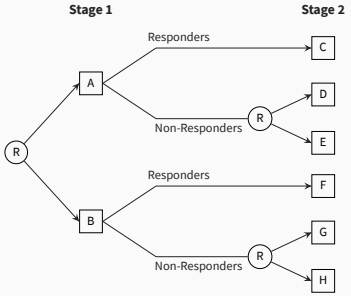
$$\left(\mathrm{E}\left[\boldsymbol{Y}_i^{(d)} \mid R_i^{(d)} = 1 \right] - \boldsymbol{\mu}^{(d)} \right) \left(\boldsymbol{\mu}^{(d)} - \boldsymbol{\mu}^{(d')} \right)^{\top}$$

is “small”

Sample Size for an End-of-Study Comparison

Under the working assumptions,

$$n \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\delta^2} \cdot \mathrm{DE}(\boldsymbol{r}) \cdot \omega(\rho, T, T_2)$$



$$\mathrm{DE}(\boldsymbol{r}) = 2 - \frac{(r_1 + r_{-1})}{2}$$

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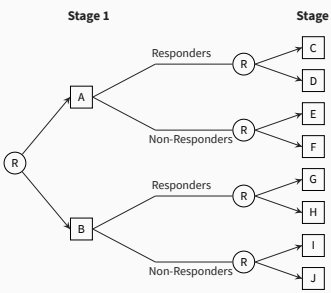
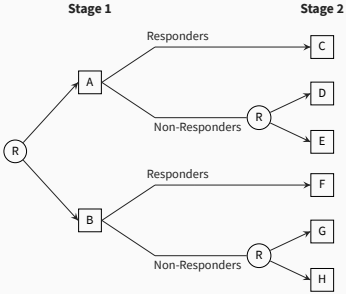
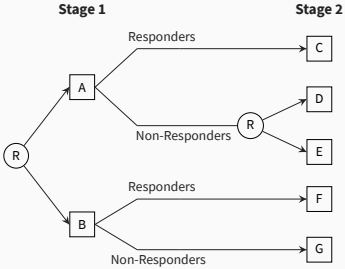


$$\mathrm{DE}(\boldsymbol{r}) = 2$$

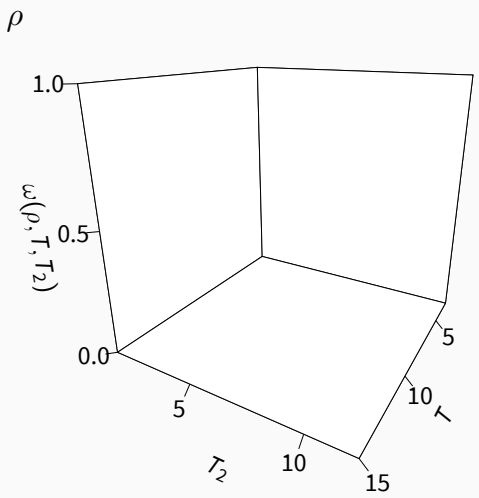


$$\mathrm{DE}(\boldsymbol{r}) = 2 - \frac{(r_1 + r_{-1})}{2}$$



$$\mathrm{DE}(\boldsymbol{r}) = \frac{1}{2}(3 - r_1)$$

Understanding $\omega(\rho, T, T_2)$

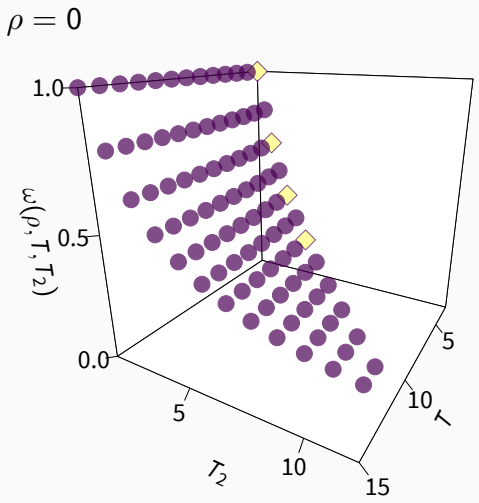


Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	
	5	2	
	7	5	
	9	7	

Understanding $\omega(\rho, T, T_2)$



Sample sizes for

- 40% response rate
- 80% power
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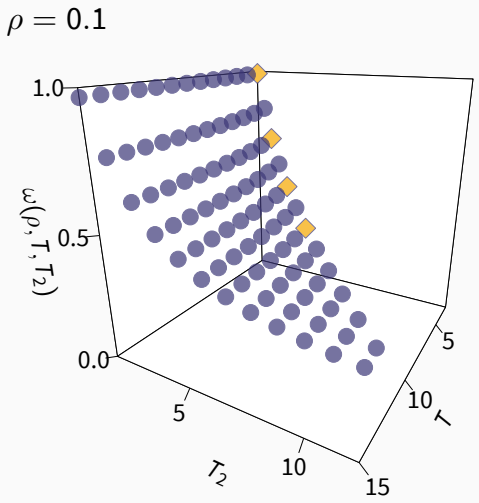
δ	T	T_2	n
0.3	3	1	559
	5	2	391
	7	5	293
	9	7	233

Understanding $\omega(\rho, T, T_2)$



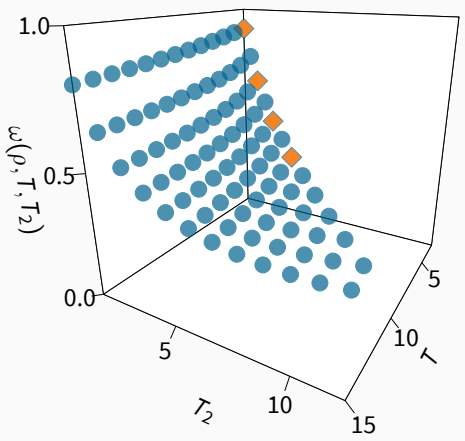
Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	553
	5	2	402
	7	5	314
	9	7	260

Understanding $\omega(\rho, T, T_2)$

$\rho = 0.3$



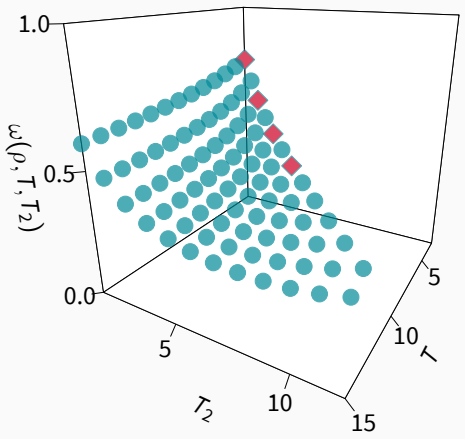
Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	508
	5	2	391
	7	5	322
	9	7	281

Understanding $\omega(\rho, T, T_2)$

$\rho = 0.5$

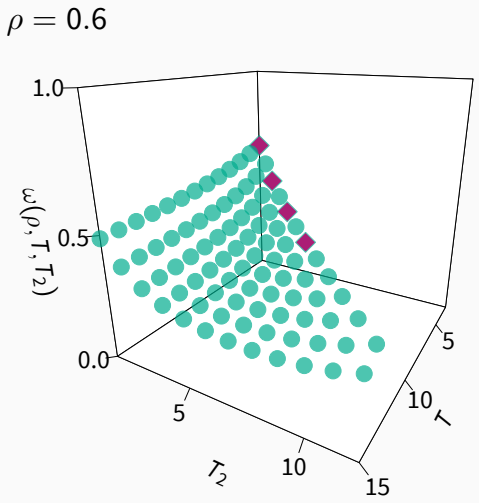


Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	419
	5	2	335
	7	5	286
	9	7	256

Understanding $\omega(\rho, T, T_2)$

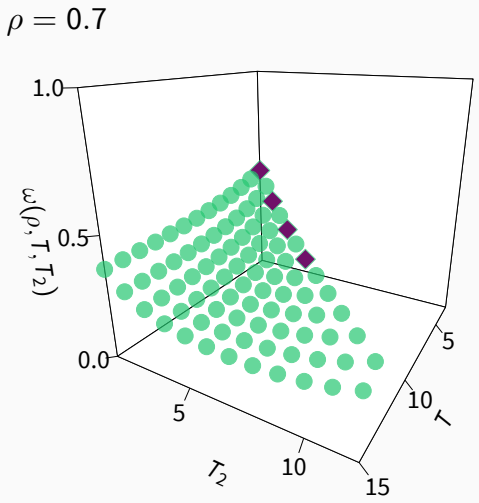


Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	358
	5	2	291
	7	5	251
	9	7	227

Understanding $\omega(\rho, T, T_2)$

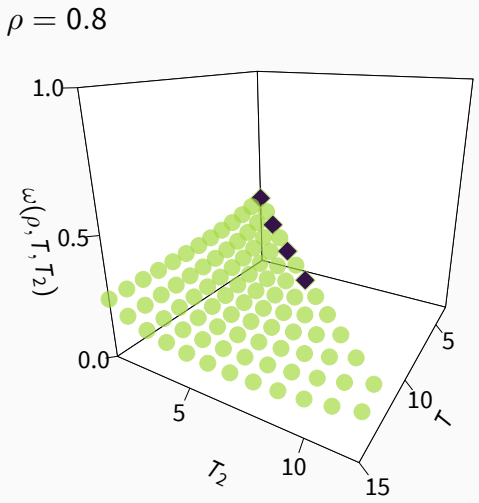


Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	285
	5	2	235
	7	5	205
	9	7	187

Understanding $\omega(\rho, T, T_2)$



Sample sizes for

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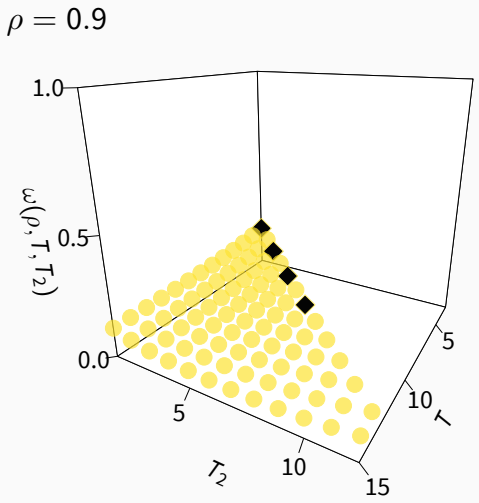
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	201
	5	2	168
	7	5	148
	9	7	136

Understanding $\omega(\rho, T, T_2)$

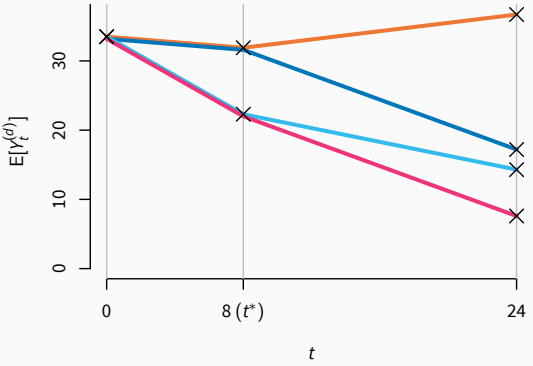


Sample sizes for

- 40% response rate
- 80% power
- 5% two-sided type-I error

δ	T	T_2	n
0.3	3	1	107
	5	2	90
	7	5	80
	9	7	74

Special Case: $\omega(\rho, T, T_2)$ simplifies for 3 measurements



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

Seewald, N. J. et al. (2020). *Stat Methods Med Res*.

Fitzmaurice, G. M., Laird, N. M., and Ware, J. H. (2011). *Applied Longitudinal Analysis*, ch. 20.

Implementation in Software

Sample size methods are implemented in an R package called *longsmart*

```
longsmart::smart_size(n = NULL, delta = 0.3, mTimes = c(0, 1, 2, 3, 4),
                      tStar = 2, power = 0.8, pR = c(0.4, 0.4))

#      Longitudinal SMART power calculation
#
#                n = 462
#            delta = 0.3
#        sig.level = 0.05
#            power = 0.8
#      alternative = two.sided
#       meas.times = 0, 1, 2, 3, 4
#           t.star = 0.5
#              rho = 0
#               pR = 0.4, 0.4
```

(Preliminary) Simulation Results

				$T = 3$		$T = 5, T_2 = 2$	
δ	ρ	r_1	r_{-1}	n	Power	n	Power
0.3	0	0.4	0.4	559	0.804	462	0.788
		0.6	0.6	489	0.825	405	0.758*
	0.3	0.4	0.4	508	0.803	427	0.804
		0.6	0.6	445	0.810	373	0.770*
	0.6	0.4	0.4	358	0.833*	296	0.818
		0.6	0.6	313	0.818	259	0.738*
	0.8	0.4	0.4	201	0.858*	164	0.842*

Recap: Our Contribution

Easy-to-use sample size formula for comparing embedded DTRs at the end of the study in a longitudinal SMART:

$$n \geq \frac{4\left(z_{1-\alpha/2} + z_{1-\gamma}\right)^2}{\delta^2} \cdot \mathrm{DE}\left(\boldsymbol{r}\right) \cdot \omega(\rho, T, T_2)$$

Cost Considerations for Longitudinal SMARTs

Trials are Expensive

- Variability in cost related to number of participants, sites, and visits
- One trial studying depression in patients with type 2 diabetes spent $1358/patient on recruitment
- Per-patient costs are an important component of overall trial costs

---

Martin, L. et al. (2017). *Nat Rev Drug Discov*.

Myers, B. A. et al. (2019). *Trials*.

Sertkaya, A. et al. (2016). *Clin Trials*.

Minimizing Recruitment Costs

- Equivalent to minimizing sample size
- Possibly of interest for hard-to-reach populations

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Naive strategy: measure the outcome as many times as possible!

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- Possibly of interest for hard-to-reach populations

Naive strategy: measure the outcome as many times as possible!

This is not practical.

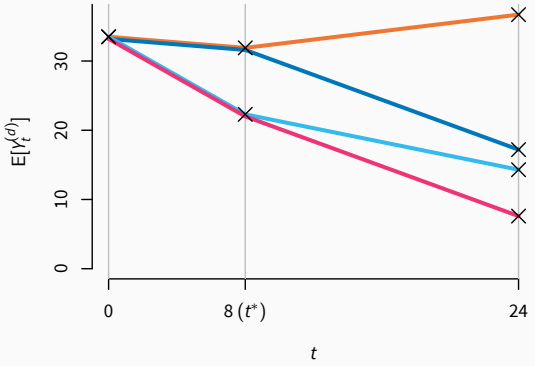
Minimizing Sample Size Requirements given T

Idea:
Given ρ and T, find the optimal allocation of measurements across stages of the SMART to minimize the sample size requirement.

$$\begin{aligned} \underset{T_2}{\text{minimize}} \quad & \omega\left(\rho, T, T_2\right) \\ \text{subject to} \quad & T_2 \in \{1, \ldots, T-2\} \end{aligned}$$

Minimizing Sample Size Requirements given T

Question: How do we allocate measurement occasions across stages of the SMART to minimize the sample size requirement?



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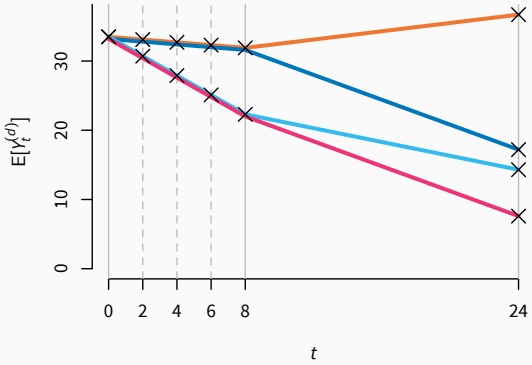

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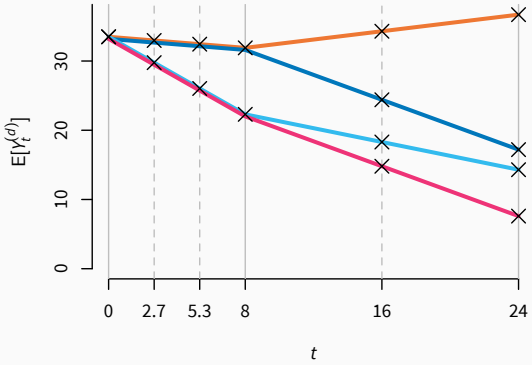

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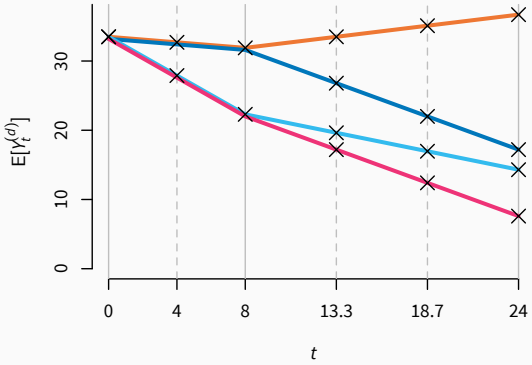
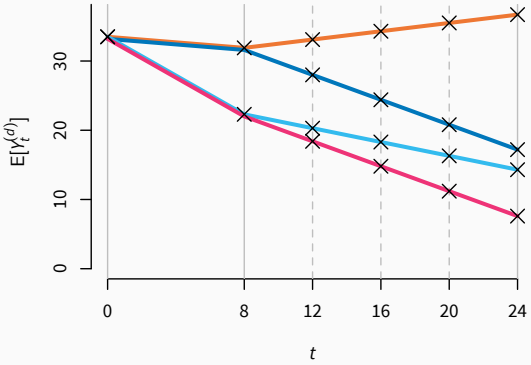
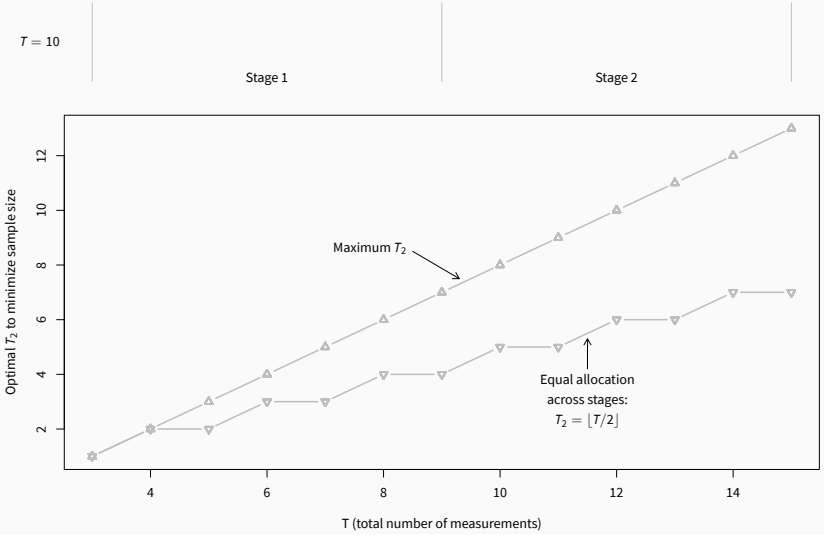


Minimizing Sample Size Requirements given T

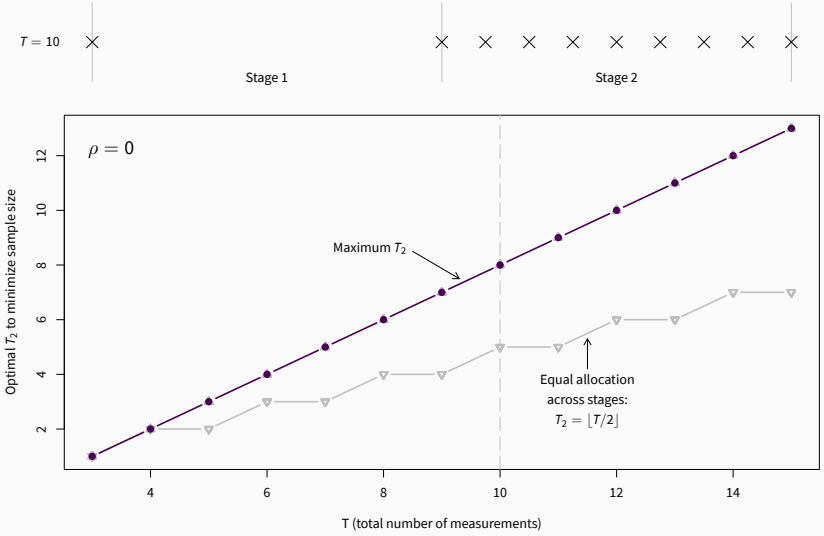
Question: How do we allocate measurement occasions across stages of the SMART to minimize the sample size requirement?



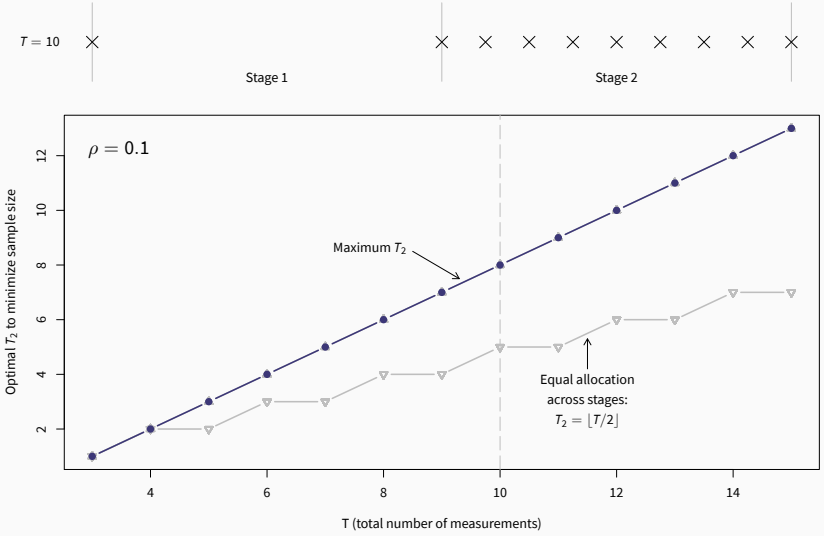
Choosing T_2 to Minimize Sample Size



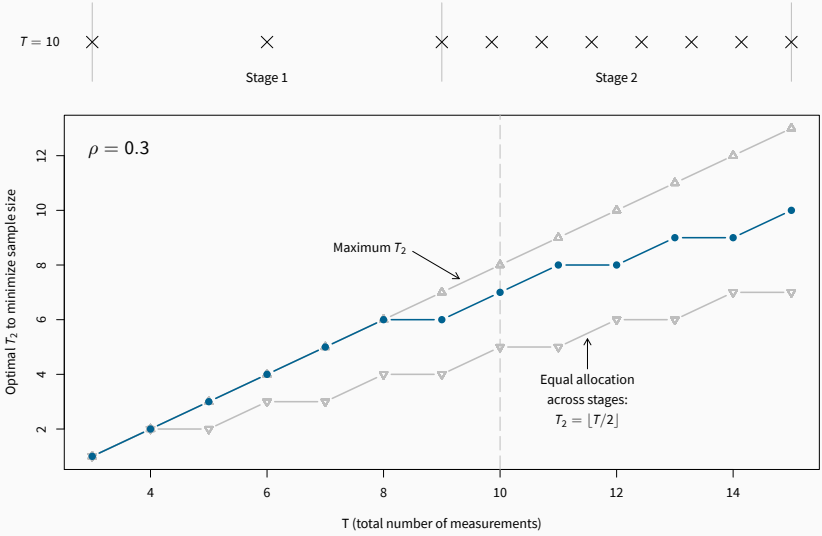
Choosing T_2 to Minimize Sample Size



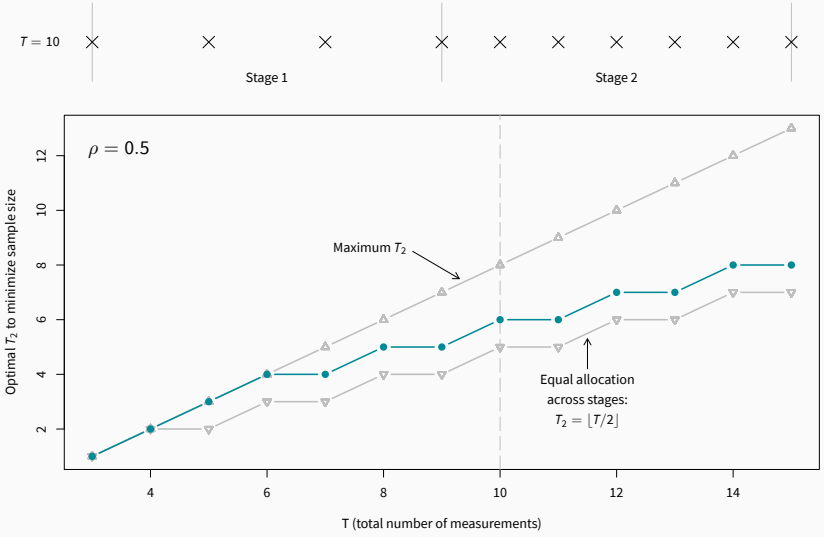
Choosing T_2 to Minimize Sample Size



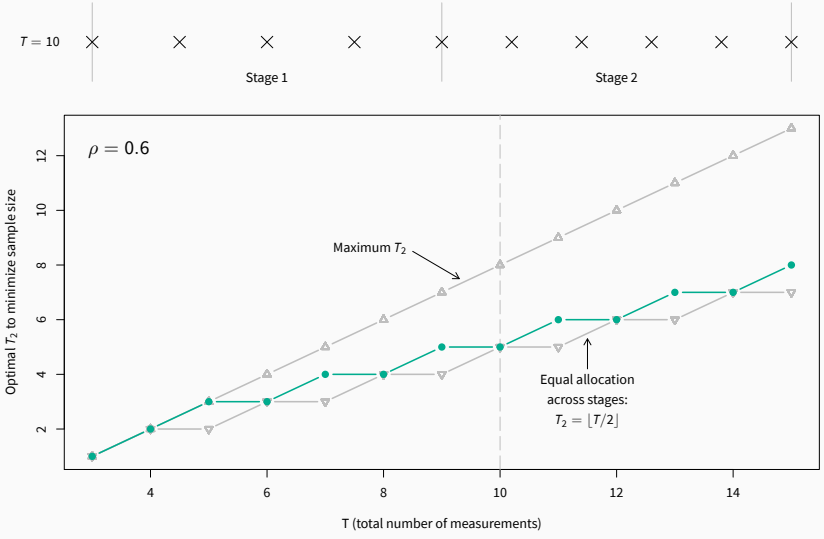
Choosing T_2 to Minimize Sample Size



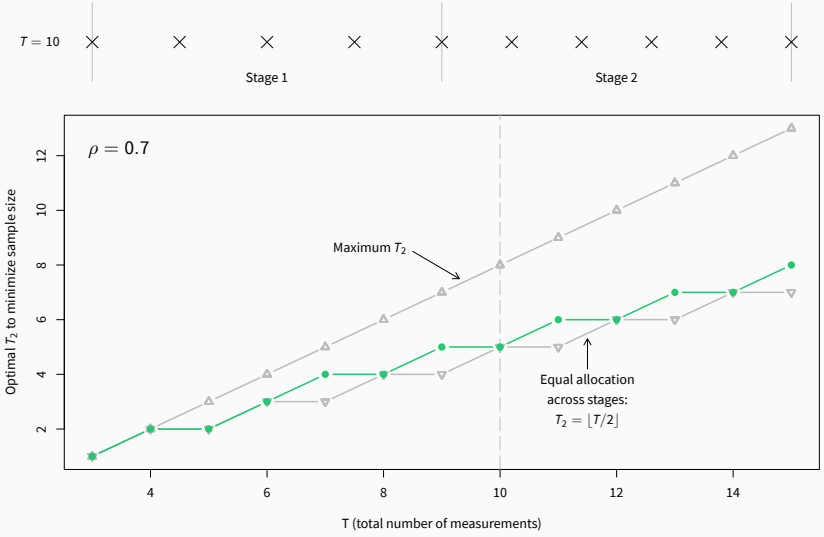
Choosing T_2 to Minimize Sample Size



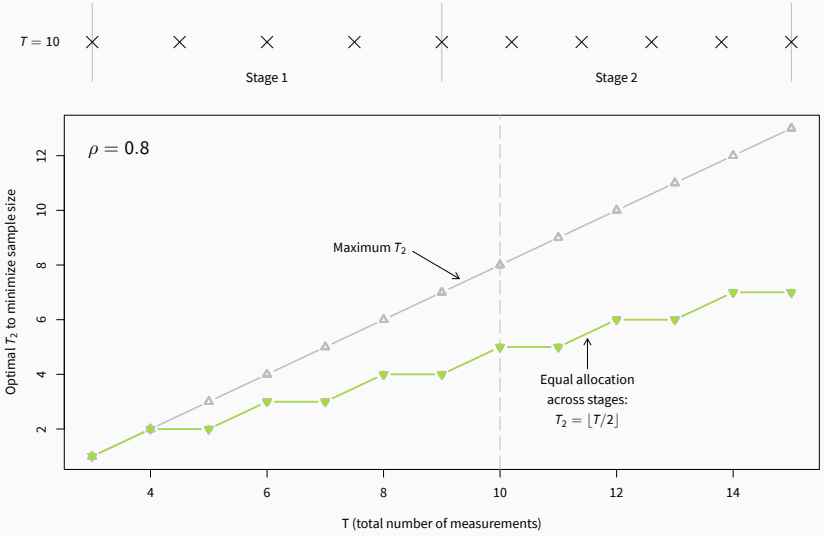
Choosing T_2 to Minimize Sample Size



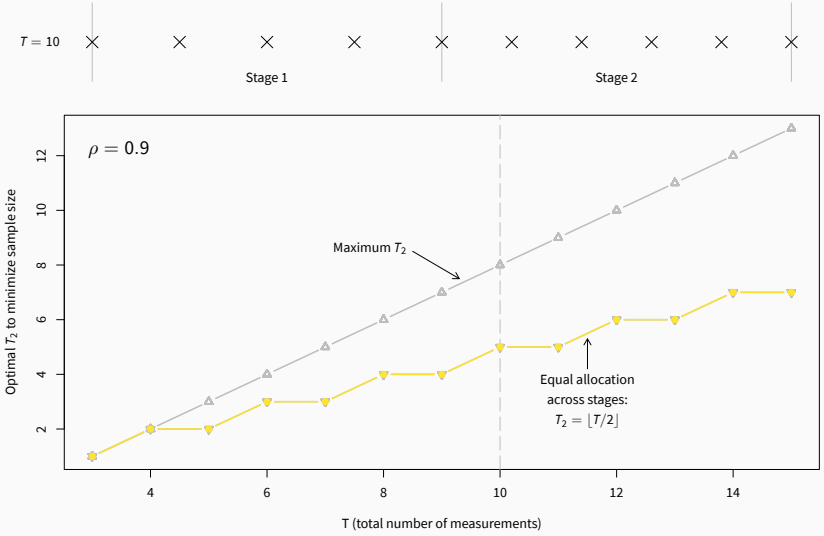
Choosing T_2 to Minimize Sample Size



Choosing T_2 to Minimize Sample Size



Choosing T_2 to Minimize Sample Size



Choosing T_2 to Minimize Sample Size

With equally-spaced measurements,

- For low ρ and/or low T, put as many measurements in stage 2 as possible.
  - At low ρ, power gains are likely from better modeling the linear trend in stage 2

Choosing T_2 to Minimize Sample Size

With equally-spaced measurements,

- For low ρ and/or low T, put as many measurements in stage 2 as possible.
  - At low ρ, power gains are likely from better modeling the linear trend in stage 2
- For higher ρ and/or higher T, diminishing returns of more measurements in stage 2
  - At high ρ, more information per measurement; share the love with stage 1

Choosing T_2 to Minimize Sample Size

With equally-spaced measurements,

- For low ρ and/or low T, put as many measurements in stage 2 as possible.
  - At low ρ, power gains are likely from better modeling the linear trend in stage 2
- For higher ρ and/or higher T, diminishing returns of more measurements in stage 2
  - At high ρ, more information per measurement; share the love with stage 1
- Difficult to identify exactly what "low ρ" and "high T" mean, since $\omega(\rho, T, T_2)$ is complicated.

Implementation in Software

longsmart has a simple interface for this optimization.

Example 1
Minimize total recruitment costs for a SMART with

- 8 measurement occasions
- $\delta = 0.4$
- $\rho = 0.36$
- $P(R = 1 \mid A_1 = 1) = 0.4$
- $P(R = 1 \mid A_1 = -1) = 0.5$
- \$300 to recruit one participant

Implementation in Software

```
longsmart::optimize_cost(delta = 0.4, tStar = 8, tMax = 16, numTimesMax = 8,
                         power = 0.8, pR = c(0.4, 0.5),
                         cost_recruit = 300)


#       Cost-optimal measurement time allocation for longitudinal SMART
#
# Optimal total number of measurements:  8
# Optimal number of measurements in stage 2:  5
# Sample size required:  160
# Total cost:  48,000
```

Per-Participant Costs in SMARTs

- Recruiting participants is expensive
- We can use efficiency from longitudinal data to lower sample size requirements
- But measurements also contribute to trial cost

Per-Participant Costs in SMARTs

- Recruiting participants is expensive
- We can use efficiency from longitudinal data to lower sample size requirements
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Goal:
Given information about recruitment and measurement costs, identify the cheapest way to achieve target power for end-of-study comparison of embedded DTRs.

Minimizing Per-Participant Costs in SMARTs

Setup

- C_R: Cost of recruiting one participant
- C_1: Per-participant cost of measuring outcome once in stage 1
- C_2: Per-participant cost of measuring outcome once in stage 2

Minimizing Per-Participant Costs in SMARTs

Setup

- C_R: Cost of recruiting one participant
- C_1: Per-participant cost of measuring outcome once in stage 1
- C_2: Per-participant cost of measuring outcome once in stage 2

Total per-participant cost

$$C(n, T, T_2) = n\left(C_R + (T - T_2)C_1 + T_2C_2\right)$$

Minimizing Per-Participant Costs in SMARTs

Find n, T, and T_2 which minimize the cost function while achieving at least 80% power.

$$\begin{aligned} \underset{n,T,T_2}{\text{minimize}} \quad & C(n, T, T_2) \\ \text{subject to} \quad & \text{power} \geq 0.8 \\ & T \in \{3, 4, \ldots, T^{\max}\}, \\ & T_2 \in \{1, 2, \ldots, T-2\} \end{aligned}$$

Minimizing Per-Participant Costs in SMARTs

Find n, T, and T_2 which minimize the cost function while achieving at least 80% power.

Substitute n with our sample size formula to satisfy the power constraint.

$$\underset{T,T_2}{\text{minimize}} \quad \left\lceil \frac{4\left(z_{1-\alpha/2} + z_{0.8}\right)^2}{\delta^2} \cdot \text{DE}(\boldsymbol{r}) \cdot \omega(\rho, T, T_2) \right\rceil \left(C_R + (T - T_2)C_1 + T_2 C_2\right)$$

$$\text{subject to} \quad T \in \{3, 4, \ldots, T^{\max}\},$$
$$T_2 \in \{1, 2, \ldots, T^{\max} - 2\}.$$

Minimizing Per-Participant Costs in SMARTs

	T^{cost} (T_2^{cost})			
C_R/C_M	$\rho = 0$	$\rho = 0.3$	$\rho = 0.5$	$\rho = 0.7$
1				
2				
5				
10				
100				

Minimizing Per-Participant Costs in SMARTs

	T^{cost} (T_2^{cost})			
C_R/C_M	$\rho = 0$	$\rho = 0.3$	$\rho = 0.5$	$\rho = 0.7$
1	3 (1)	3 (1)	3 (1)	3 (1)
2	15 (13)	3 (1)	3 (1)	3 (1)
5	15 (13)	7 (5)	5 (3)	15 (7)
10	15 (13)	15 (10)	15 (8)	15 (7)
100	15 (13)	15 (10)	15 (8)	15 (7)

Implementation in Software

longsmart has a simple interface for this optimization.

Example 2
Minimize total costs for a SMART with

- At most 8 measurement occasions
- $\delta = 0.4$
- $\rho = 0.36$
- $P(R = 1 \mid A_1 = 1) = 0.4$
- $P(R = 1 \mid A_1 = -1) = 0.5$
- \$300 to recruit one participant
- \$20 to measure one participant once

Implementation in Software

```
longsmart::optimize_cost(delta = 0.4, tStar = 8, tMax = 16, numTimesMax = 8,
                         power = 0.8, pR = c(0.4, 0.5),
                         cost_recruit = 300, cost_meas = 20)


#       Cost-optimal measurement time allocation for longitudinal SMART
#
# Optimal total number of measurements:  8
# Optimal number of measurements in stage 2:  5
# Sample size required:  160
# Total cost:  73,600
```

Practical Implications for Designing SMARTs

- Reframe conversations about sample size for longitudinal SMARTs
- Statisticians can work collaboratively with investigators to design more cost-effective trials

Bloch, D. A. (1986). *Statistics in Medicine*; Zhang, S. and Ahn, C. (2011). *Statistics in Biopharmaceutical Research*; Liu, J. and Colditz, G. A. (2017). *Biometrical Journal*.

Practical Implications for Designing SMARTs

- Reframe conversations about sample size for longitudinal SMARTs
- Statisticians can work collaboratively with investigators to design more cost-effective trials
- Different framing from previous work which constrains *cost*
- We prioritize the reality that trials need at least 80% for funding

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Bloch, D. A. (1986). *Statistics in Medicine*; Zhang, S. and Ahn, C. (2011). *Statistics in Biopharmaceutical Research*; Liu, J. and Colditz, G. A. (2017). *Biometrical Journal*.

Conclusions and Looking Ahead

A Suite of Tools

We have developed a suite of tools for the design and analysis of longitudinal SMARTs

- Sample size for comparison of embedded DTRs
- Financial considerations
- R package for simulation and sample size

Future Extensions

- Other longitudinal estimands (like area under the curve)
- Intensive longitudinal data

Thank you.