Mixed effect models to compare dynamic treatment regimens with SMART data

Brook Luers
Department of Statistics, University of Michigan
luers@umich.edu
brookluers.com

ENAR
March 26, 2019

Summary

Mixed models can be used to make causal comparisons of dynamic treatment regimens using longitudinal data from a SMART.

SMART: multi-stage randomized trial; enables causal comparison of dynamic treatment regimens (sequences of treatment decisions)

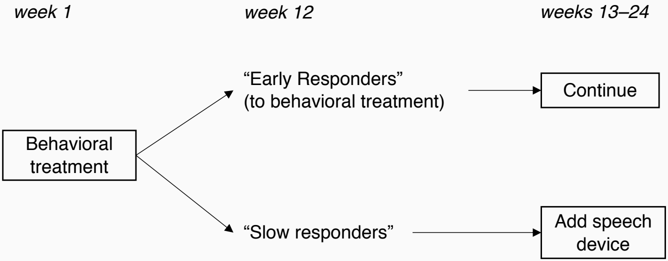
Outline

- Background: DTRs, SMARTs
- A mixed model for longitudinal SMARTs
  - estimation: weighted, pseudo-likelihood
  - inverse probability weights; but they are random
  - mean estimator is robust to misspecified random effects
  - random effects prediction
- Data analysis using example SMART in autism

Background: DTRs, SMARTs

What is a dynamic treatment regimen (DTR)?

A sequence of rules for deciding how to provide treatment over time

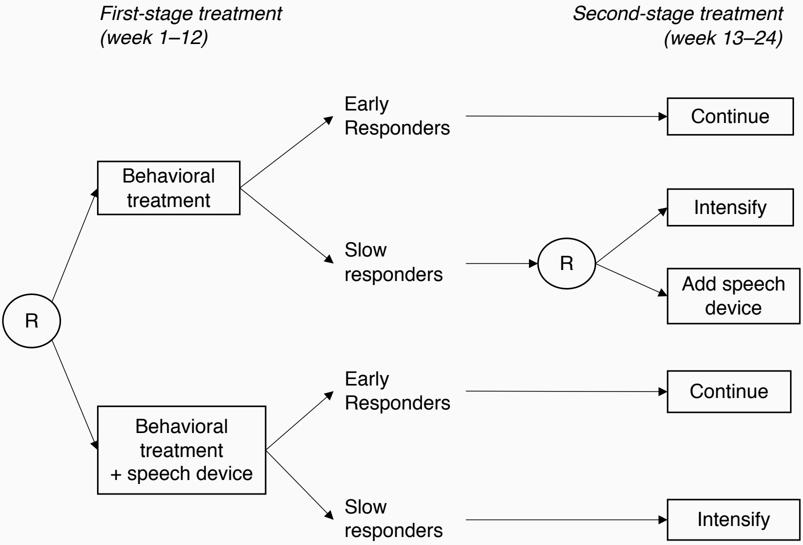


Kasari et al. [2014]

Given current patient information, what treatment is provided next?

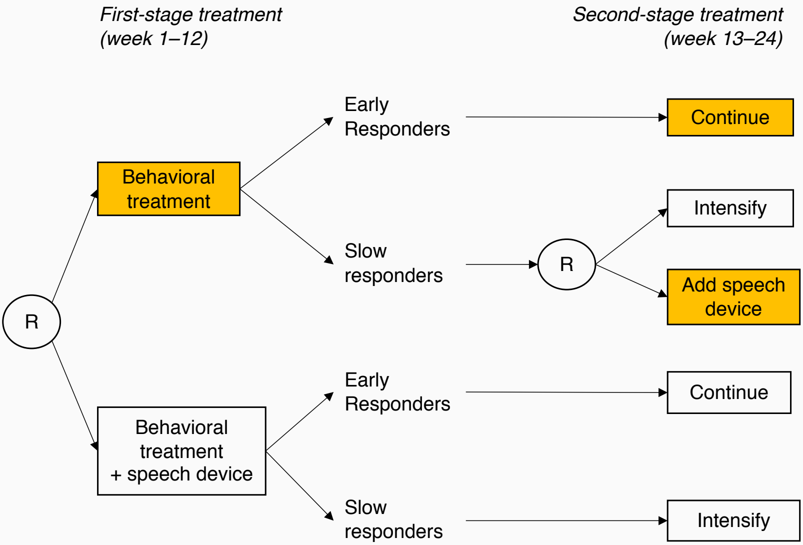
One treatment regimen, multiple treatment sequences

SMART: a trial design for comparing DTRs



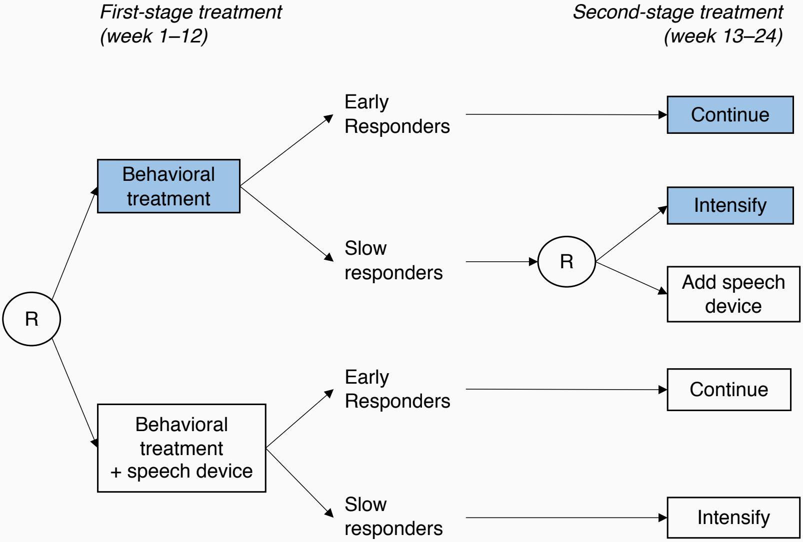
SMART: a trial design for comparing DTRs

Three DTRs are embedded in this trial



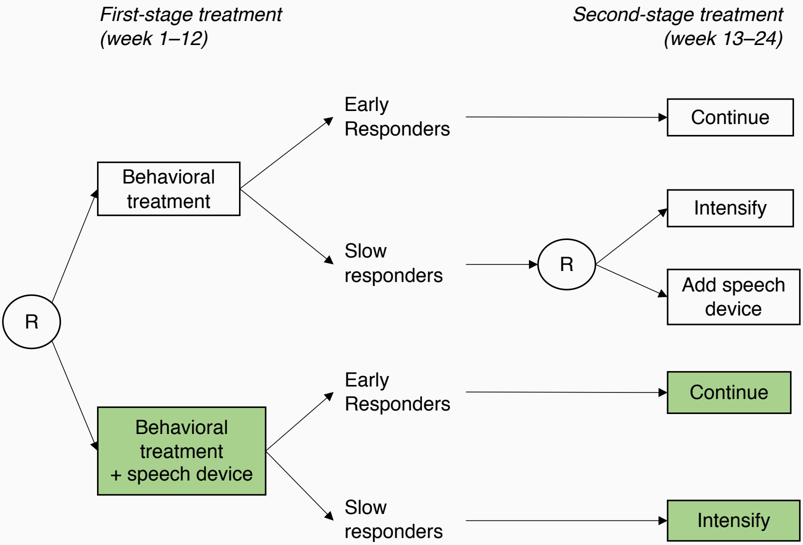
SMART: a trial design for comparing DTRs

Three DTRs are embedded in this trial

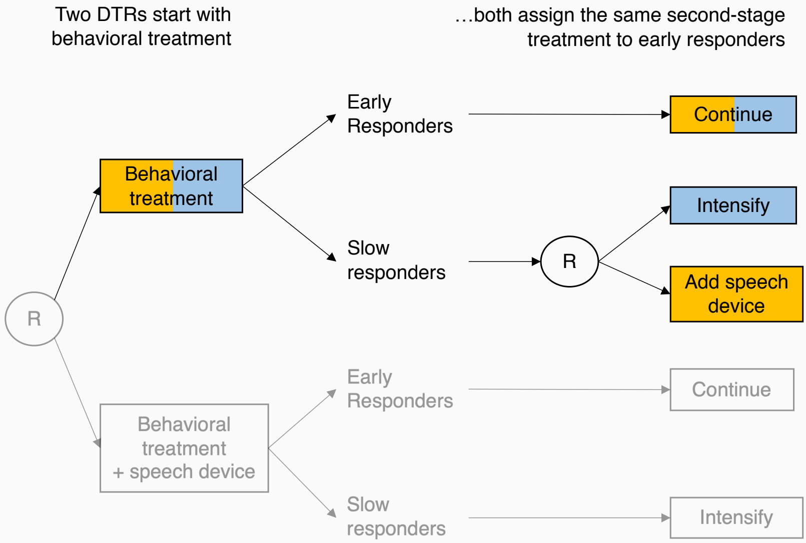


SMART: a trial design for comparing DTRs

Three DTRs are embedded in this trial



A treatment sequence observable under two DTRs



Scientific aim: causal comparisons of DTRs

Identify the best dynamic treatment regimen using longitudinal data from a SMART.

Other scientific aims are possible

- e.g. Which first-stage treatment is best?

Statistical framework

for making causal comparisons among DTRs

$Y_i^{(a_1,a_2)}$: vector of longitudinal potential outcomes under (a_1, a_2)

(a_1, a_2): fixed treatment regimen, not a random variable

Compare DTRs by estimating, for each (a_1, a_2),

$$\mathbb{E}\left(Y_i^{(a_1,a_2)} \mid L_i\right),$$

the mean outcome had the entire population followed (a_1, a_2).

Marginal over $R_i^{(a_1)}$: "slow/early responder"

$L_i =$ vector of baseline covariates

Statistical framework: modeling assumptions

Focus on linear models for continuous $Y_i^{(a_1,a_2)}$

$$\mathbb{E}\left(Y_i^{(a_1,a_2)} \mid L_i\right) = X_i^{(a_1,a_2)}\beta$$

$X_i^{(a_1,a_2)}$: $n_i \times p$ design matrix for the ith participant
with n_i observation times $t_{i1}, \ldots, t_{in_i}$

a function of $t_{ij}, (a_1, a_2),$ and L_i (baseline covariates)

Causal comparisons, e.g.

$$\mathbb{E}\left(Y_i^{(a_1,a_2)} \mid L_i\right) - \mathbb{E}\left(Y_i^{(b_1,b_2)} \mid L_i\right)$$

are functions of β.

A mixed model for longitudinal SMARTs

The model

$$Y_i^{(a_1,a_2)} = X_i^{(a_1,a_2)}\beta + Z_i b_i + \epsilon_i$$

Z_i : $n_i \times q$ random effects design matrix

b_i : q-dimensional random effects vector

$\epsilon_i \sim N(0, \sigma^2 I_{n_i})$ is independent of $b_i \sim N(0, G)$

i.e.

$$Y_i^{(a_1,a_2)} \mid L_i, b_i \sim N\left(X_i^{(a_1,a_2)}\beta + Z_i b_i, \sigma^2 I_{n_i}\right)$$

$$Y_i^{(a_1,a_2)} \mid L_i \sim N\left(X_i^{(a_1,a_2)}\beta, Z_i G Z_i^{\intercal} + \sigma^2 I_{n_i}\right)$$

Why mixed models?

- Familiar tool for longitudinal data analysis, not yet available for SMARTs
- Flexible parametrization of $\mathrm{Var}\left(Y_i^{(a_1,a_2)} \mid L_i\right)$
  - function of covariates
  - parsimonious: # parameters does not depend on n_i
  - potential efficiency gains
- Assess subject-to-subject variation
  - subject-specific trajectories via random effects prediction ("BLUP")
  - separate variance parameters for subject-level variation

Model parameters

$$Y_i^{(a_1,a_2)} = X_i^{(a_1,a_2)}\beta + Z_i b_i + \epsilon_i$$

$$\implies V_i := \mathrm{Var}\left(Y_i^{(a_1,a_2)} \mid L_i\right) = Z_i G Z_i^{\mathsf{T}} + \sigma^2 I_{n_i}$$

Parameters:

- β: p-dimensional vector of mean parameters
- α: vector of unique parameters in $V_i = V_i(\alpha)$.

Notation for observed data

Random treatment assignments: A_{1i}, A_{2i}

By design of the SMART,

$$A_{1i} = a_1 \in \{1, -1\} \text{ with prob. } \mathbb{P}(A_{1i} = a_1)$$

$$A_{2i} = a_2 \in \{1, -1\} \text{ with prob. } \mathbb{P}(A_{2i} = a_2 \mid A_{1i}, R_i = 0)$$

(only non-responders are randomized twice)

Denote

$$R_i \in \{0, 1\} : \text{ observed response status}$$

$$Y_i : \text{ observed longitudinal outcome}$$

$$i = 1, \ldots, N \text{ participants}$$

Estimation: causal assumptions

We do not observe the potential outcomes

$$Y_i^{(a_1,a_2)},\ R_i^{(a_1)} \text{ (binary response status)}$$

for all (a_1, a_2).

So we assume

$$R_i = \sum_{a_1} \mathbb{1}_{[A_{1i}=a_1]} R_i^{(a_1)}$$

$$Y_i = R_i Y_i^{(A_{1i})} + (1 - R_i) Y_i^{(A_{1i},A_{2i})}$$

$$\left.\begin{aligned} Y_i^{(a_1,a_2)} &\perp\!\!\!\perp A_{1i} \\ R_i^{(a_1)} &\perp\!\!\!\perp A_{1i} \\ Y_i^{(a_1,a_2)} &\perp\!\!\!\perp A_{2i} \mid A_{1i}, R_i \end{aligned}\right\} \text{ satisfied by design}$$

Estimation: weighted, pseudo-likelihood

If we observed $Y_i^{(a_1,a_2)}$ for all (a_1, a_2),
we could compute MLEs using likelihood for $Y_i^{(a_1,a_2)}$

Since we only observe Y_i, compute

$$\hat{\alpha}, \hat{\beta} = \arg\max_{\alpha,\beta} -\frac{1}{2} \sum_i \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) f_i(\alpha, \beta, a_1, a_2)$$

$$\begin{aligned} f_i(\alpha, \beta, a_1, a_2) := {} & \log\det(V_i(\alpha)) \\ & + (Y_i - X_i^{(a_1,a_2)}\beta)^\intercal V_i(\alpha)^{-1}(Y_i - X_i^{(a_1,a_2)}\beta) \end{aligned}$$

Estimation: weighted, pseudo-likelihood

Can solve for $\hat{\beta}$

$$\hat{\beta}(\alpha) = \left(\sum_i \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) X_i^{(a_1,a_2)\intercal} V_i(\alpha)^{-1} X_i^{(a_1,a_2)}\right)^{-1} \left(\sum_i \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) X_i^{(a_1,a_2)\intercal} V_i(\alpha)^{-1} Y_i\right)$$

In practice,

$$\hat{\alpha} = \arg\max_{\alpha} -\frac{1}{2} \sum_i \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) f_i(\alpha, \hat{\beta}(\alpha), a_1, a_2)$$

$$\hat{\beta} = \hat{\beta}(\hat{\alpha})$$

Weights: a function of $(A_{1i}, R_i, A_{2i}, a_1, a_2)$

The function is known by design, but $\tilde{W}_i$ is a random variable

$$\tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) = W_i(A_{1i}, R_i, A_{2i}, a_1, a_2)C_i(A_{1i}, R_i, A_{2i}, a_1, a_2)$$

$$\begin{aligned} &W_i(A_{1i}, R_i, A_{2i}, a_1, a_2) \\ &\quad := \frac{1}{\mathbb{P}(A_{1i} = a_1)} \left(R_i + \frac{(1 - R_i)}{\mathbb{P}(A_{2i} = a_2 \mid A_{1i}, R_i = 0)} \right) \end{aligned}$$

$$\begin{aligned} &C_i(A_{1i}, R_i, A_{2i}, a_1, a_2) \\ &\quad := \begin{cases} 1 & \text{if } A_{1i}, R_i, A_{2i} \text{ observable under } (a_1, a_2) \\ 0 & \text{otherwise} \end{cases} \end{aligned}$$

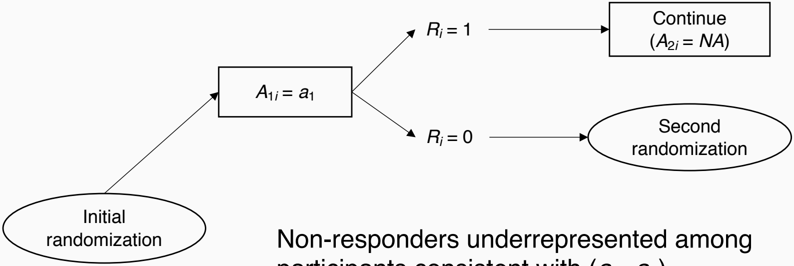
Weights: a function of $(A_{1i}, R_i, A_{2i}, a_1, a_2)$

Suppose $a_1, a_2 \in \{1, -1\}$, and

$$\mathbb{P}(A_{1i} = a_1) = 0.5, \qquad \mathbb{P}(A_{2i} = a_2 \mid A_{1i}, R_i = 0) = 0.5.$$

For the fixed regimen (a_1, a_2),

$$W_i(A_{1i}, R_i, A_{2i}, a_1, a_2) = \begin{cases} 4 & \text{if } R_i = 0 \\ 2 & \text{if } R_i = 1 \end{cases}$$



Non-responders underrepresented among participants consistent with (a_1, a_2)

Properties of $\hat{\beta}$

consistent, asymptotically Gaussian even if V_i misspecified

i.e. random effects $Z_i b_i$ can be misspecified

Estimate of $\mathrm{Var}\left(\hat{\beta}\right)$: $\frac{1}{N}\hat{J}^{-1}\hat{I}\hat{J}^{-1}$

$$\hat{J} = \frac{1}{N}\sum_i \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) X_i^{(a_1,a_2)\intercal} \hat{V}_i(\hat{\alpha})^{-1} X_i^{(a_1,a_2)}$$

$$\hat{I} = \frac{1}{N}\sum_i \hat{U}_i \hat{U}_i^{\intercal}$$

$$\hat{U}_i = \sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2) X_i^{(a_1,a_2)\intercal} \hat{V}_i(\hat{\alpha})^{-1} (Y_i - X_i^{(a_1,a_2)}\hat{\beta}).$$

Random effects prediction

Compute a prediction based on the weighted pseudo-likelihood:

$$\begin{aligned}\hat{b}_i &:= \hat{b}_i(\hat{\alpha}, \hat{\beta}) \\ &= \frac{\sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2)\hat{G}Z_i^\intercal \hat{V}_i^{-1}(Y_i - X_i^{(a_1,a_2)}\hat{\beta})}{\sum_{a_1,a_2} \tilde{W}_i(A_{1i}, R_i, A_{2i}, a_1, a_2)}\end{aligned}$$

Motivated by

$$\mathbb{E}\left(b_i \mid Y_i^{(a_1,a_2)}, X_i^{(a_1,a_2)}\right) = GZ_i^\intercal V_i^{-1}(Y_i^{(a_1,a_2)} - X_i^{(a_1,a_2)}\beta)$$

Other statistical methods for SMARTs

Longitudinal SMARTs: weighted, GEE-like estimators

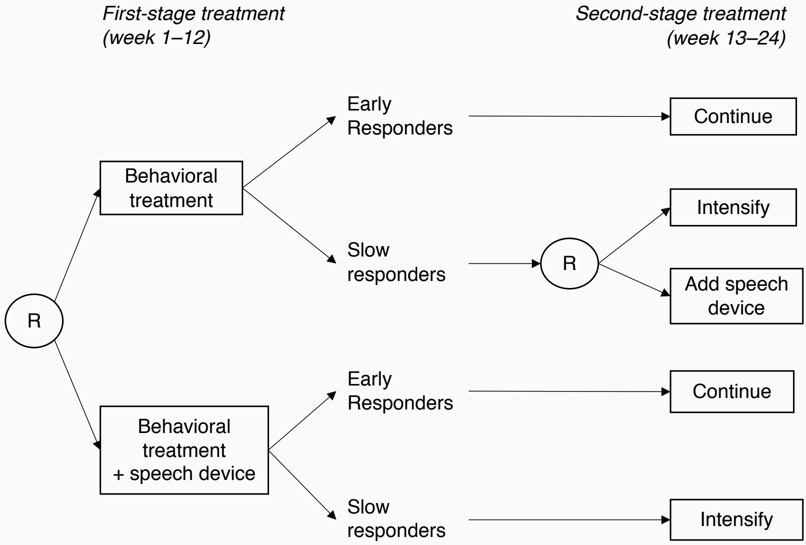
- Lu et al. [2016], Li [2017], Seewald et al. [2018], Dziak et al. [2019]
- Working model for variance-covariance, sandwich standard errors

General references

- Murphy [2005], Nahum-Shani et al. [2012], Almirall et al. [2014]

Data analysis: example SMART in autism

Recall the autism SMART design



A piecewise linear model with random intercept

Three DTRs: $(1,1),(1,-1),(-1,1)$

Y_{ij} : number of “socially communicative utterances”

$t_{ij} \in \{0,12,24,36\}$ weeks, $\quad N = 61$

$$\begin{aligned}\mathbb{E}\left(Y_{ij}^{(a_1,a_2)} \mid X_{ij}^{(a_1,a_2)}, b_i\right) = \beta_0 &+ t_j^{[0,12]}\left(\beta_1 + \beta_2 a_1\right) \\ &+ t_j^{(12,36]}\left(\beta_3 + \beta_4 a_1 + \beta_5 \mathbb{1}_{[a_1=1]} a_2\right) \\ &+ \beta_6 \mathtt{age}_i + b_i,\end{aligned}$$

where

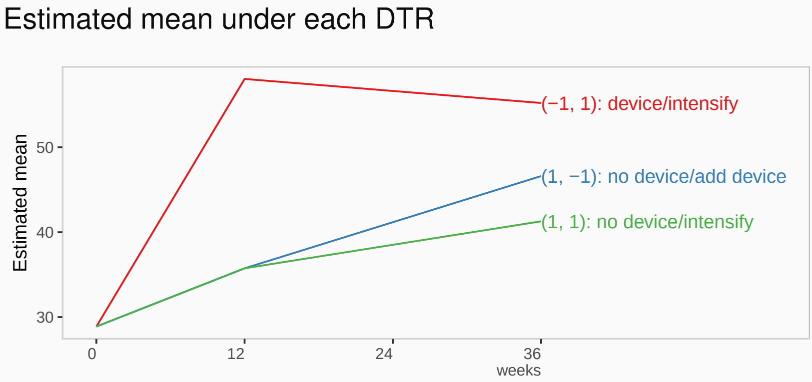
$$t_j^{[0,12]} = \left(t_j \mathbb{1}_{[t_j \le 12]} + 12\mathbb{1}_{[t_j > 12]}\right)$$

$$t_j^{(12,36]} = (t_j - 12)\mathbb{1}_{[t_j > 12]}$$

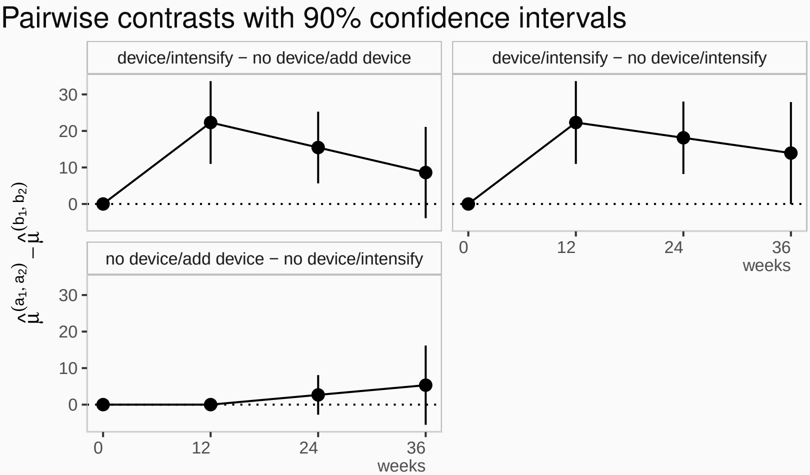
$$\mathtt{age}_i = \text{age at baseline}$$

$$b_i \sim N(0, \sigma_b^2): \text{ random intercept}$$

Primary aim: compare DTRs

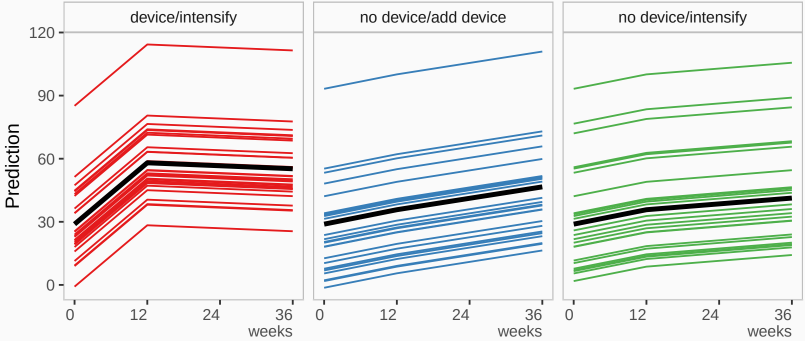


Primary aim: compare DTRs



Person-specific predictions

$$X_i^{(a_1,a_2)}\hat{\beta} + Z_i\hat{b}_i$$



$$\hat{\sigma} = 21$$

$$\hat{\sigma}_b = 24$$

Next steps

- Prove $\hat{b}_i$ has minimum MSE
- Software implementation
  - currently using “tricks” valid only with integer weights
- Scenarios when Z_i can include (a_1, a_2), so that V_i depends on (a_1, a_2)
- Advantages of mixed models for missing data in SMARTs

Thank you

Download slides: `brookluers.com/research`

Coauthors

Min Qian (Columbia University)

Inbal Nahum-Shani (University of Michigan)

Connie Kasari (University of California, Los Angeles)

Daniel Almirall (University of Michigan)

References

D. Almirall, I. Nahum-Shani, N. Sherwood, and S.A. Murphy. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *Translational Behavioral Medicine*, 4(3):260–274, 2014.

John J. Dziak, Jamie Yap, Daniel Almirall, James R. McKay, Kevin G. Lynch, and Inbal Nahum-Shani. A data analysis method for using longitudinal binary outcome data from a SMART to compare adaptive interventions. *Multivariate Behavioral Research*, pages 1–24, 2019. URL `https://doi.org/10.1080/00273171.2018.1558042`.

Connie Kasari, Ann Kaiser, Kelly Goods, Jennifer Nietfeld, Pamela Mathy, Rebecca Landa, Susan Murphy, and Daniel Almirall. Communication interventions for minimally verbal children with autism: A sequential multiple assignment randomized trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 53(6): 635–646, 2014.

Zhiguo Li. Comparison of adaptive treatment strategies based on longitudinal outcomes in sequential multiple assignment randomized trials. *Statistics in Medicine*, 36(3):403–415, 2017.

Xi Lu, Inbal Nahum-Shani, Connie Kasari, Kevin G. Lynch, David W. Oslin, William E. Pelham, Gregory Fabiano, and Daniel Almirall. Comparing dynamic treatment regimes using repeated-measures outcomes: modeling considerations in smart studies. *Statistics in Medicine*, 35(10):1595–1615, 2016.

References (continued)

S.A. Murphy. An experimental design for the development of adaptive treatment strategies. *Statistics in Medicine*, 24(10):1455–1481, May 2005.

I. Nahum-Shani, M. Qian, D. Almirall, W.E. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu, and S.A. Murphy. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological Methods*, 17: 457–477, 2012.

Nicholas J. Seewald, Kelley M. Kidwell, Inbal Nahum-Shani, Tianshuang Wu, James R. McKay, and Daniel Almirall. Sample size considerations for comparing dynamic treatment regimens in a sequential multiple-assignment randomized trial with a continuous longitudinal outcome. *arXiv e-prints*, art. arXiv:1810.13094, Oct 2018.