Bayesian Set of Best Dynamic Treatment Regimes and Sample Size Determination for SMARTs with Binary Outcomes

William J Artman
Department of Biostatistics and Computational Biology,
University of Rochester Medical Center,
Rochester, Saunders Research Building, 265 Crittenden Blvd., NY 14642, USA
William_Artman@URMC.Rochester.edu

Ashkan Ertefaie
Department of Biostatistics and Computational Biology,
University of Rochester Medical Center,
Rochester, Saunders Research Building, 265 Crittenden Blvd., NY 14642, USA

Kevin G Lynch
Center for Clinical Epidemiology and Biostatistics (CCEB)
and Department of Psychiatry,
University of Pennsylvania,
3535 Market Street, 5099, Philadelphia, PA 19104, USA

James R McKay
Department of Psychiatry, Perelman School of Medicine,
University of Pennsylvania,
3535 Market St., Suite 500, Philadelphia, PA 19104, USA

Abstract
One of the main goals of sequential, multiple assignment, randomized trials (SMART) is to find the most efficacious design embedded dynamic treatment regimes. The analysis method known as multiple comparisons with the best (MCB) allows comparison between dynamic treatment regimes and identification of a set of optimal regimes in the frequentist setting for continuous outcomes, thereby, directly addressing the main goal of a SMART. In this paper, we develop a Bayesian generalization to MCB for SMARTs with binary outcomes. Furthermore, we show how to choose the sample size so that the inferior embedded DTRs are screened out with a specified power. We compare log-odds between different DTRs using their exact distribution without relying on asymptotic normality in either the analysis or the power calculation. We conduct extensive simulation studies under two SMART designs and illustrate our method’s application to the Adaptive Treatment for Alcohol and Cocaine Dependence (ENGAGE) trial.
1 Introduction

Substance use disorders are a common yet debilitating group of conditions for which treatment response is highly variable (McKay, 2009; Kranzler & McKay, 2012; Black & Chung, 2014; Witkiewitz et al., 2015). While there exist interventions, physicians often must rely on clinical experience to choose subsequent therapies for individuals who have failed to respond to initial treatment. In order to personalize medicine, there is a need for longitudinal trial data as well as methodologies for comparing sequences of treatment decision rules.

Sequential, multiple assignment, randomized trial (SMART) designs are a type of longitudinal clinical trial specifically designed to determine the optimal sequence of decision rules called dynamic treatment regimes (DTRs) (Lavori et al., 2000; Murphy, 2005; Lei et al., 2012; Rose et al., 2019; Murphy et al., 2001; Murphy, 2003; Robins, 2004; Nahum-Shani et al., 2012; Chakraborty & Moodie, 2013; Chakraborty & Murphy, 2014; Laber et al., 2014). In particular, there are DTRs embedded in the SMART by design; hence, SMARTs provide evidence for the regime tailored to a subject’s response.

Standard multiple comparison approaches used to control for type I errors result in a loss of statistical power. This is critically important when working with smaller data sets such as clinical trials. Ertefaie et al. (2015) introduced a frequentist semiparametric model for estimation of the embedded DTR outcomes as well as continuous outcome multiple comparisons with the best (MCB) for comparing the embedded DTRs. MCB enables the construction of a set of optimal embedded DTRs which are statistically indistinguishable for the available data. MCB offers increased power while controlling the type I error rate so that the best embedded DTR is included with a specified probability (Hsu, 1981, 1984, 1996; Artman et al., 2018). By requiring only $L - 1$ comparisons where $L$ is the number of embedded DTRs compared with all $\binom{L}{2}$ pairwise comparisons, MCB yields greater power over other methods. However, applications of MCB have focused on continuous outcomes.

Binary outcomes arise frequently as primary outcomes in psychiatry and addiction clinical trials. The exiting methods for estimation in SMARTs with binary outcomes do not permit complex comparisons between all of the embedded DTRs such as with MCB (Kidwell et al., 2018; Dziak et al., 2019). Moreover, the power analysis approaches for a SMART almost entirely focus on continuous outcomes aiming to size a SMART for simple comparisons between two embedded DTRs or to power a SMART so that the best embedded DTR has the largest point estimate with a specified probability (Crivello et al., 2007a,b). More
recently, Rose et al. (2019) proposed a method which relies on Q-learning for continuous outcomes to size a SMART. Kidwell et al. (2018) developed a sample size calculator for binary outcome SMARTs, but their method is restricted to comparisons between only two embedded DTRs. Furthermore, they assume asymptotic normality which may not hold due to the small sample size of embedded treatment sequences in a SMART.

Yan et al. (2020) developed a frequentist sample size calculation method for pilot SMARTs. In particular, they size a SMART so that the mean outcome of a DTR is within “a margin of error”. In other words, so that confidence intervals are less than a pre-specified length. Advantages of their method include applicability to continuous, count, and binary outcomes. A limitation is that normality is assumed for all outcome summary statistics including log-OR. However, this may be unreasonable due to the small sample size in each branch of the SMART. This could be problematic especially in a pilot SMART for which the sample size is small by design. An advantage of our method is it does not make such strong parametric assumptions and uses uninformative priors to avoid bias. An important similarity of their method to ours is taking into account uncertainty in sample size calculations rather than only viewing the problem as that of estimation. In addition, for our method, the best embedded DTR will be included with a given probability. In summary, our method makes comparisons between > 2 embedded DTRs adjusting for multiplicity, rather than looking at them marginally. The authors of Yan et al. (2020) emphasize if there is no hypothesis testing in the pilot SMART, then standard power analysis is not relevant. Therefore, their method fills an important gap for pilot SMARTs. However, in this article, we are interested in drawing inference on the optimal embedded DTRs and sizing SMARTs for this purpose.

Ogbagaber et al. (2016) presented a method for power analysis based off an omnibus test as well as all pairwise comparisons for continuous outcomes. Artman et al. (2018) proposed a power analyses for SMARTs using MCB approach. Specifically, the latter method computes the number of individuals to enroll in a SMART in order to achieve a specified power to exclude embedded DTRs inferior to the best by a given amount from the set of best. This approach, however, relies on the normality assumption of the outcome, and thus, cannot always be used with binary outcomes.

In this article, we extend MCB to the Bayesian binary outcome setting to directly address current methods’ limitations. We build upon the work in Artman et al. (2018) to develop a rigorous power analysis procedure. We simulate from the posterior of each parameter for each treatment sequence individually which are independent. This circumvents the need for specifying the correlation matrix of the random embedded DTR outcomes in the frequentist setting. Then, using Robin’s G-computation formula for a dynamic regime (Robins, 1986), we represent each embedded DTR outcome as a weighted average of the independent treatment sequences. We use the transformed draws in the MCB procedure to facilitate Bayesian
inference. We leverage the method in Mandel & Betensky (2008) to extend the MCB methodology to use Monte Carlo draws in the construction of the set of best embedded DTRs. In particular, it enables the construction of simultaneous one-sided upper credible intervals for log-odds ratios, comparing each embedded DTR to the best embedded DTR when the outcome is binary. Our proposed approach obviates many of the challenges associated with the current methods of choice, namely

(i) in contrast with the method of Artman et al. (2018), our Bayesian MCB method can be used directly with binary outcomes and our power analysis requires fewer parameter specification;

(ii) in contrast with the existing multiple comparison approaches, our approach performs fewer comparisons which increases the statistical power; and

(iii) is designed specifically for statistical inference for complex comparisons of > 2 embedded DTRs and is applicable to small sample size.

In Section 2, we introduce the ENGAGE SMART. In Section 3, we formalize notation and present our Bayesian binary outcome model. In Section 4, we provide details about about Bayesian MCB. We then show how to perform power analysis. In Section 5, simulation studies are conducted. In Section 6, we illustrate our method on the the real ENGAGE SMART. In Section 7, we outline how to choose the input parameters for sample size determination. In Section 8, we conclude with discussion. The Appendix provides proofs.

2 The ENGAGE trial

In the Adaptive Treatment for Alcohol and Cocaine Dependence SMART (ENGAGE; Figure 1), individuals were initially randomized to two different treatments: motivational interviewing (MI) for intensive outpatient programs (IOP) and for patient’s choice (PC). PC consisted of an intervention which the patient chooses. Patients who were non-engagers (did not attend any therapy sessions) at 2 weeks were enrolled. After 8 weeks, those who failed to attend any sessions during weeks 7 and 8 were classified as non-responders/non-engagers and were re randomized to either MI-PC or No Further Care (NFC). Those who were still responders were assigned to NFC. The original study analysis suggested that MI-IOP was significantly more effective than MI-PC. In this paper, we analyze the SMART to compare embedded DTRs. We restrict our attention in the study to individuals who did not engage by week 2 which yielded a sample size 148. One of the main goals of SMART designs is the identification of the best embedded DTRs for a primary outcome (Nahum-Shani et al. 2012). We construct a binary outcome which is whether the log of the total number of drinking days plus cocaine use days was less than the 25th percentile of the log of the total number of drinking days plus cocaine use days.
Determination of optimal embedded DTRs would provide evidence-based recommendations for clinicians when treating individual patients with substance use disorders. The ENGAGE study aimed to determine the optimal treatment for non-responders (McKay et al., 2015; Van Horn et al., 2015). There were four embedded DTRs. Two of the embedded DTRs were as follows:

1. Start with MI+IOP. If the subject is engaged during the first 8 weeks, then at the 8-week point, offer NFC; if the subject is labeled as a non-engager at week 8 of follow-up, offer MI+PC.

2. Start with MI+IOP. If the subject is engaged during the first 8 weeks, then at the 8-week point, offer NFC; if the subject is labeled as a non-engager at week 8 of follow-up, offer NFC.

The other two embedded DTRs are similar (see Table 1). See McKay et al. (2015); Van Horn et al. (2015) for more details about the SMART.

### 3 Framework

#### 3.1 Notation

We focus on a SMART in which there are two stages where at each stage, individuals are randomized to different treatment options. By design, stage-2 treatment is commonly tailored based on a patient’s ongoing
response status which generates the different embedded DTRs (see Figures 1 and 2). Let $Y^{(l)}$ denote the binary potential outcome for an individual following embedded DTR $l \in \{1, \ldots, L\}$. Let $Y_k$ denote the binary potential outcome for an individual following treatment sequence $k \in \{1, \ldots, K\}$. Let $A_1 \in \{-1, +1\}$ denote the stage-1 treatment assignment indicator. Let $A_2^{R} \in \{-1, +1\}$ denote the stage-2 treatment assignment indicator for responders and $A_2^{NR} \in \{-1, +1\}$ be the treatment assignment indicator for non-responders. Let $S_i$ denote the observed stage-1 treatment response indicator. Let $\theta^{(l)}$ be the probability of response in the $l^{th}$ embedded DTR, $l = 1, \ldots, L$, where we assume that the $L^{th}$ embedded DTR is the best. Let $\theta_k$ denote the probability of response in the $k^{th}$ treatment sequence, $k = 1, \ldots, K$. Let $Z_i \in \{1, \ldots, K\}$ denote the treatment sequence indicator for subject $i$.

Then, the log-odds ratio for the $l^{th}$ embedded DTR compared with the best embedded DTR is $\zeta^{(l)} = \log \left( \frac{\text{Odds}^{(l)}}{\text{Odds}^{(L)}} \right) = \log(\text{Odds}^{(l)}) - \log(\text{Odds}^{(L)})$ and $\text{Odds}^{(l)} = \frac{\theta^{(l)}}{1 - \theta^{(l)}}$. We do not make any distributional assumptions about the log-odds or the log-odds ratio. Assuming that being equal to 1 is the desirable outcome, higher log-odds (and equivalently, log-odds ratios) implies superiority of the corresponding embedded DTR.

### 3.2 Binary outcome models

We assume observations $Y_{i}^{obs} \overset{iid}{\sim} \text{Bern}(\theta_{Z_i})$ where $Z_i$ is the treatment sequence followed by the $i^{th}$ individual and $S_i \overset{iid}{\sim} \text{Bern}(\lambda_{A_1})$ for $i = 1, \ldots, n$ where $A_1$ is the stage-1 treatment. Our target parameter is the probability of response at the end of the trial ($Y^{(l)} = 1$) for a particular embedded DTR. Using Robins’ G-computation
\[
\begin{array}{|c|c|}
\hline
\text{Embedded Dynamic Treatment Regime} & \\
1 & A_1 = +1, S = 1 \text{ or } A_1 = +1, S = 0, A_2 = +1 \\
& \text{Receive MI-IOP, if respond receive NFC, if not respond switch to MI-PC} \\
2 & A_1 = +1, S = 1 \text{ or } A_1 = +1, S = 0, A_2 = -1 \\
& \text{Receive MI-IOP, if respond, receive NFC, if not respond, receive NFC} \\
3 & A_1 = -1, S = 1 \text{ or } A_1 = -1, S = 0, A_2 = +1 \\
& \text{Receive MI-PC, if respond receive NFC, if not respond switch to MI-PC} \\
4 & A_1 = -1, S = 1 \text{ or } A_1 = -1, S = 0, A_2 = -1 \\
& \text{Receive MI-PC, if respond receive NFC, if not respond, receive NFC.} \\
\hline
\end{array}
\]

Table 1: Embedded dynamic treatment regime decision rules for the ENGAGE trial. MI-IOP: motivational interviewing for intensive outpatient program. MI-PC: motivational interviewing for patient choice. NFC: no further care.

The formula \cite{Robins1986}, we have the following representation for the target parameter:

\[
\Pr(Y^{(l)} = 1) = \Pr(Y = 1 \mid A_1 = a_{1l}, S = 1, A_2^R = a_{2l}) \Pr(S = 1 \mid A_1 = a_{1l}) + \\
\Pr(Y = 1 \mid A_1 = a_{1l}, S = 0, A_2^{NR} = a_{2l}) \Pr(S = 0 \mid A_1 = a_{1l}), \; l = 1, 2, \ldots, L. \tag{1}
\]

Thus, the mean outcome under each embedded DTR is a weighted average of the responder treatment sequence outcome and the non-responder treatment sequence outcome. This permits estimation and inference without using a marginal structural model. While baseline covariates could be included in \cite{} for the purpose of power analysis, we define the target parameter as a marginalized quantity. In our Bayesian procedure, we impose a non-informative prior on \( \theta_k \) and \( \lambda_{A_1} \), which results in beta posterior distributions. We then define the treatment sequence response probabilities \( \theta_R = \Pr(Y = 1 \mid A_1 = a_{1l}, S = 1, A_2^R = a_{2l}) \), \( \theta_{NR} = \Pr(Y = 1 \mid A_1 = a_{1l}, S = 0, A_2^{NR} = a_{2l}) \). Lastly, the probability of response in stage 1 for those assigned to \( A_1 \) is given by \( \lambda_{A_1} = \Pr(S = 1 \mid A_1 = a_{1l}) \). We leverage \cite{} to transform each MCMC draw to the target parameter and, subsequently, into a log-odds ratio. By taking this simulation-based approach, we avoid making normality assumptions. At the \( m \)th iteration of the MCMC, we draw \( \theta_{R,m}, \theta_{NR,m}, \) and \( \lambda_{A_1,m} \). Hence, the \( m \)th draw of the probability of response for the \( l \)th embedded DTR is \( \theta_{m}^{(l)} = \theta_{R,m} \lambda_{A_1,m} + \theta_{NR,m} (1 - \lambda_{A_1,m}) \).

The \( m \)th draw of the log-odds ratio is \( \zeta_{m}^{(l)} = \log \text{OR}^{(l)} = \log \left( \frac{\theta_{m}^{(l)}}{1 - \theta_{m}^{(l)}} \right) - \log \left( \frac{\theta_{m}^{(L)}}{1 - \theta_{m}^{(L)}} \right) \). Next, we specify the likelihoods. The likelihood for the observed end-of-study outcomes is given by the following \( f(Y_1, ..., Y_n \mid \theta_1, ..., \theta_k) \propto \prod_{i=1}^{n} \theta_{Z_i}^{Y_i} (1 - \theta_{Z_i})^{1 - Y_i} \), where the treatment sequence indicator is \( Z_i \in \{1, ..., K\} \). We then assume a non-informative uniform prior on \( \theta_k \), \( k \in \{1, ..., K\} \) which yields the posterior of \( \theta_k \) given by the
Table 2: Embedded dynamic treatment regime decision rules for the General SMART.

| Rule | Decision | Condition 1 | Condition 2 | Action 1 | Action 2 |
|------|----------|-------------|-------------|----------|----------|
| 1    | Receive Trt. 1 | $A_1 = +1, S = 1, A_2^R = +1$ or $A_1 = +1, S = 0, A_2^{NR} = +1$ | | if respond, continue Trt 1, if not respond, switch to Trt 4 |
| 2    | Receive Trt. 1 | $A_1 = +1, S = 1, A_2^R = +1$ or $A_1 = +1, S = 0, A_2^{NR} = -1$ | | if respond, continue Trt 1, if not respond, add Trt 4 |
| 3    | Receive Trt. 1 | $A_1 = +1, S = 1, A_2^R = -1$ or $A_1 = +1, S = 0, A_2^{NR} = +1$ | | if respond, add Trt 3, if not respond, switch to Trt 4 |
| 4    | Receive Trt. 2 | $A_1 = -1, S = 1, A_2^R = +1$ or $A_1 = -1, S = 0, A_2^{NR} = +1$ | | if respond, continue Trt. 2, if no respond, add Trt 4 |
| 5    | Receive Trt. 2 | $A_1 = -1, S = 1, A_2^R = -1$ or $A_1 = -1, S = 0, A_2^{NR} = -1$ | | if respond, continue Trt. 2, if not respond, add Trt 4 |
| 6    | Receive Trt. 2 | $A_1 = -1, S = 1, A_2^R = -1$ or $A_1 = -1, S = 0, A_2^{NR} = -1$ | | if respond, add Trt 3, if not respond, add Trt 4 |

Furthermore, the posterior of the stage-1 response probabilities are given by

$$f(\lambda_{A_1} | S_1, ..., S_n) = \text{Beta} \left( \sum_{i:A_1 = A_1} S_i + 1, \sum_{i:A_1 = A_1} 1 - \sum_{i:A_1 = A_1} S_i + 1 \right)$$

Theorem 1. Let $\zeta^{(l)}_{m}, l = 1, \cdots, L, m = 1, \cdots, M$ denote draws of the parameters $\zeta^{(l)}$ obtained from 4 MCB for binary outcomes

4.1 Simultaneous credible intervals for Monte Carlo draws

In this section, we describe our MCB procedure based off Mandel & Betensky (2008) to construct simultaneous 100(1 – α)% one-sided upper credible intervals using multivariate draws from an arbitrary distribution. Their method was originally designed to construct confidence intervals for draws obtained using the bootstrap. In Section A.1. of the Appendix, we show that the latter approach is also applicable to Monte Carlo simulation draws of the posterior. The following theorem forms the basis for the extension of MCB to the Bayesian setting.

Theorem 1. Let $\zeta^{(l)}_{m}, l = 1, \cdots, L, m = 1, \cdots, M$ denote draws of the parameters $\zeta^{(l)}$ obtained from
Monte Carlo simulation. Let \( r(m, l) \) denote the rank of \( \zeta_m^{(l)} \) and assume no ties. Then, \( U^{(l)} = \zeta_{(r_{1-\alpha}l)}^{(l)} \), \( l = 1, \cdots, L - 1 \) are simultaneous \( 1 - \alpha \) level upper credible intervals for \( \zeta^{(l)}, l = 1 \cdots, L - 1 \) where \( r_{1-\alpha} \) is the \((1 - \alpha)^{th}\) quantile of \( \max_i r(m, l) \) for each draw \( m = 1, \cdots, M \).

The goal is to construct upper credible interval limits \( U^{(l)}, \ l = 1, \cdots, L \) which jointly have coverage \( 1 - \alpha \). Note that there is a one-to-one correspondence between a draw \( \zeta_m^{(l)} \) and its rank \( r(m, l) \) in the absence of ties where \( m \) is the \( m^{th} \) draw, \( m = 1, \cdots, M \). In particular, \( \zeta_{(r(m, l))}^{(l)} = \zeta_m^{(l)} \). Then, \( \zeta_m^{(l)} \) is less than \( U^{(l)} \) for all \( l = 1, \cdots, L \) for \( 100(1 - \alpha)\% \) of the draws \( m = 1, \cdots, M \) if and only if \( \zeta_{(r(m, l))}^{(l)} \) is less than \( U^{(l)} \) for all \( l = 1, \cdots, L \) for \( 100(1 - \alpha)\% \) of the draws \( m = 1, \cdots, M \). A sufficient condition is for \( r(m, l) \) to be less than some integer \( r_{1-\alpha} \) for all \( l, \) for \( 100(1 - \alpha)\% \) of the \( r(m, l), \ l = 1, \cdots, L, \ m = 1, \cdots, M \). Equivalently, the max rank across embedded DTRs \( r(m) := \max_i r(m, l) \) is less than \( r_{1-\alpha} \) for \( 100(1 - \alpha)\% \) of the draws \( m = 1, \cdots, M \). Let \( r_{1-\alpha} \) equal the \( 1 - \alpha \) quantile of \( r(1), \cdots, r(M) \). Then, letting \( U^{(l)} = \zeta_{(r_{1-\alpha}l)}^{(l)} \) for \( l = 1, \cdots, L \) completes the proof. See the Appendix for more details. The proof that the algorithm works assumes no ties. When there are ties in rank, one can use the minimum rank to obtain coverage near \( 100(1 - \alpha)\% \) for a sufficiently large number of draws (Mandel & Betensky 2008).

Define \( \hat{\mathcal{B}} = \{ EDTR^{(l)} \mid U^{(l)} \geq 0 \} \) where \( U^{(l)} \) is the upper credible limit for the difference between the \( l^{th} \) embedded DTR’s log-odds and the best embedded DTR’s log-odds. Then, regardless of sample size, \( \hat{\mathcal{B}} \) contains the true optimal embedded DTR with probability at least \( 1 - \alpha \) by construction. It furthermore adjusts for multiplicity by the above procedure. We define \( \hat{\mathcal{B}} \) to be the set of best embedded DTRs as it contains embedded DTRs which are not statistically significantly inferior to the best embedded DTR. This is analogous to MCB constructed for continuous outcomes in Ertefaie et al. (2015). Sample sizes which are larger shrink \( \hat{\mathcal{B}} \) so that inferior embedded DTRs are excluded. In the next section, we prove how to choose the sample size to achieve this goal.

### 4.2 Power calculation with binary outcomes

In the last section, we demonstrated how to construct a set of optimal embedded DTRs. In this section, we show how to size a SMART to obtain a set of embedded DTRs which are not different in their efficacy by a clinically meaningful amount. In terms of the credible intervals, those which cover 0 correspond with embedded DTRs which are not statistically distinguishable from the optimal embedded DTR. Those that are strictly below 0 are inferior and are subsequently excluded from the set of best. We present how to perform power analysis for Bayesian MCB with a binary outcomes.

Let \( \eta \) be the known inputs (response probabilities at each stage). We wish to determine the sample size
such that
\[
\Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid \eta \right) = 1 - \gamma
\]
where 1 − \gamma is the power, \Delta is the clinically meaningful difference with the best embedded DTR and \Delta_l is the log-odds ratio between the \(l^{th}\) embedded DTR and the best embedded DTR. Without loss of generality, assume that \(Y^{\text{new}}\) is a sufficient statistic for \(\eta\). Then,
\[
\Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid \eta \right) = \int \Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid Y^{\text{new}}, \eta \right) \Pr(Y^{\text{new}} \mid \eta) dY^{\text{new}}
\]
\[
= \int \int \Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid Y^{\text{new}}, \eta, \phi^{(1)}, ..., \phi^{(M)} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)} \mid Y^{\text{new}}) \Pr(Y^{\text{new}} \mid \eta) d\phi dY^{\text{new}},
\]
where \(\phi^{(1)}, ..., \phi^{(M)}\) are independent of \(\eta\) given \(Y^{\text{new}}\) by sufficiency and are draws of the parameters for which we are constructing upper credible intervals. Therefore,
\[
\int \int \Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid Y^{\text{new}}, \eta, \phi^{(1)}, ..., \phi^{(M)} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)} \mid Y^{\text{new}}) \Pr(Y^{\text{new}} \mid \eta) d\phi dY^{\text{new}}
\]
\[
= \int \int \Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)} < 0\} \mid \phi^{(1)}, ..., \phi^{(M)} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)} \mid Y^{\text{new}}) \Pr(Y^{\text{new}} \mid \eta) d\phi dY^{\text{new}}
\]
\[
= \int \int I \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)}(\phi^{(1)}, ..., \phi^{(M)}, i) < 0\} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)} \mid Y^{\text{new}}) \Pr(Y^{\text{new}} \mid \eta) d\phi dY^{\text{new}}
\]
\[
\approx \frac{1}{I_1} \sum_{i=1}^{I_1} \int I \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)}(\phi^{(1)}, ..., \phi^{(M)}, i) < 0\} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)}, i \mid Y^{\text{new}, i}) d\phi,
\]
where \(U^{(l)}(\cdot, ..., \cdot)\) maps the posterior draws to the \(k^{th}\) simultaneous credible interval as determined by the procedure in the previous section. Furthermore, \(Y^{\text{new}, i} \sim \Pr(Y^{\text{new}} \mid \eta)\) for all \(i = 1, ..., I_1\). In the above, we have used the Law of Large Numbers. Similarly,
\[
\frac{1}{I_1} \sum_{i=1}^{I_1} \int I \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)}(\phi^{(1)}, ..., \phi^{(M)}, i) < 0\} \right) \Pr(\phi^{(1)}, ..., \phi^{(M)}, i \mid Y^{\text{new}, i}) d\phi
\]
\[
\approx \frac{1}{I_1} \sum_{i=1}^{I_1} \frac{1}{J_1} \sum_{j=1}^{J_1} I \left( \bigcap_{l: \Delta_l \geq \Delta} \{U^{(l)}(\phi^{(1)}, ..., \phi^{(M)}, i) < 0\} \right),
\]
where $\phi^{(m),i}_j \sim p(\phi \mid Y^{\text{new},i})$ and $Y^{\text{new},i} \sim p(Y^{\text{new}} \mid \eta)$. In summary,

$$\Pr \left( \bigcap_{l: \Delta_l \geq \Delta} \left\{ U_l^{(i)} < 0 \right\} \mid \eta \right) \approx \frac{1}{I_1} \sum_{i=1}^{I_1} \frac{1}{J_1} \sum_{j=1}^{J_1} \mathcal{I} \left( \bigcap_{l: \Delta_l \geq \Delta} \left\{ U_l^{(i)} \left( \phi^{(1),i}_j, \ldots, \phi^{(M),i}_j \right) < 0 \right\} \right).$$

Therefore, we may choose a sample size that yields $100(1 - \gamma)$% power by the following procedure.

Specify a grid of sample sizes $n \in \{n_{\text{min}}, \ldots, n_{\text{max}}\}$. For each $n$ in the grid, compute the statistical power using steps 2-4 and for each $n$ in the grid calculate the power.

1. Draw $Y^{\text{new},i} \sim p(Y^{\text{new}} \mid \eta), i = 1, \ldots, I_1$ where the input parameters $\eta$ are given by the stage-1 treatment response probabilities and end-of-study response probabilities.
2. Draw $\phi^{(m),i}_j \sim p(\phi \mid Y^{\text{new},i})$ for all $i = 1, \ldots, I_1$ and $j = 1, \ldots, J_1, m = 1, \ldots, M$.
3. Compute $U_l^{(i)} \left( \phi^{(1),i}_j, \ldots, \phi^{(M),i}_j \right), l = 1, \ldots, L$.
4. Iterate steps 2-4, $M$ (e.g., $M = 500$) times and repeat until $n$ is sufficiently large so that

$$\frac{1}{I_1} \sum_{i=1}^{I_1} \frac{1}{J_1} \sum_{j=1}^{J_1} \mathcal{I} \left( \bigcap_{l: \Delta_l \geq \Delta} \left\{ U_l^{(i)} \left( \phi^{(1),i}_j, \ldots, \phi^{(M),i}_j \right) < 0 \right\} \right) \geq 1 - \gamma.$$

5 Simulation studies

5.1 SMART design 1 simulation study

See Figure 1 for a flow chart of the simulation design 1 SMART. Design 1 includes 6 embedded treatment sequences and 4 embedded DTRs. People who respond to their stage-1 treatment continue on the same treatment, whereas non-responders are re-randomized to one of two rescue treatments. The following is the simulation scheme:

1. Stage-1 treatment assignment: $A_1 \in \{-1, 1\}$ with probability = 0.5.
2. Stage-1 treatment response indicator: $S \sim \text{Bern}(\lambda_{A_1}), A_1 \in \{-1, +1\}$.
3. Stage-2 treatment for non-responders: $A_2 \in \{-1, 1\}$ with probability = 0.5.
4. Final binary outcome: $Y_{Z_i} \sim \text{Bern}(\pi_{Z_i}), i = 1, \ldots, n$.

5.2 General SMART simulation study

See Figure 2 for a flow chart of the simulation general SMART. The general SMART has 8 embedded treatment sequences and 8 embedded DTRs. The following is the simulation scheme:
Table 3: Simulation SMART designs with 4 embedded DTRs and one with 8, respectively. Embedded DTR performance estimates are given using our Bayesian approach compared with “weighted and replicated” logistic regression with a marginal structural model \( m(\beta, A) = \beta_0 + \beta_1 A_1 + \beta_2 A_2^R + \beta_3 A_3^{NR} + \beta_4 A_1 A_2^R + \beta_5 A_1 A_2^{NR} \) (Kidwell et al., 2018; Nahum-Shani et al., 2012; Almirall et al., 2014).

1. Stage-1 treatment assignment: \( A_1 \in \{ -1, 1 \} \) with probability = 0.5.

2. Stage-1 treatment response indicator: \( S \sim \text{Bern}(\lambda_{A_1}) \), \( A_1 \in \{ -1, +1 \} \).

3. Stage-2 treatment for responders to stage-1 treatment \( (S = 1) \): \( A_2^R \in \{ -1, 1 \} \) with probability = 0.5.

4. Stage-2 treatment for non-responders to stage-1 treatment \( (S = 0) \): \( A_2^{NR} \in \{ -1, 1 \} \) with probability = 0.5.

5. The final binary outcome is: \( Y_i \sim \text{Bern}(\pi_{Z_i}) \), \( i = 1, ..., n \).

One could incorporate covariates in either simulation scheme, but this would impose modeling assumptions which may lead to misspecification if, for example, probit or logistic regression is employed. Furthermore, including covariates would complicate the power analysis procedure as well as the interpretation of MCB. Hence, we directly simulate the variables based off the probabilities of response.
5.3 Simulation: results

Table 3 shows the bias and SD for our Bayesian estimation approach and for a frequentist approach weighted and replicated logistic regression with the marginal structural model (MSM)

\[ m(\mathbf{\beta}, \mathbf{A}) = \mathbf{\beta}_0 + \mathbf{\beta}_1 \mathbf{A}_1 + \mathbf{\beta}_2 \mathbf{A}_2^R + \mathbf{\beta}_3 \mathbf{A}_2^{NR} + \mathbf{\beta}_4 \mathbf{A}_1 \mathbf{A}_2^R + \mathbf{\beta}_5 \mathbf{A}_1 \mathbf{A}_2^{NR} \].

We see that the bias is similar between the Bayesian procedure and MSM. The Bayesian procedure has slightly smaller SE.

To compute the empirical power, we simulated 1000 datasets over a grid of sample sizes, 150, 200, ..., 500. We used 1000 Monte Carlo draws for each of the 1000 datasets to obtain 1000 upper credible interval limits for each embedded DTR, e.g., \( U_i^{(t)}, t = 1, ..., L \) and \( i = 1, ..., 1000 \) for each embedded DTR \( i \) and each sample size. We then computed the empirical power as

\[ \text{Power} \approx \frac{1}{1000} \sum_{i=1}^{1000} \mathcal{I} \left( \bigcap_{t: \Delta_t \geq \Delta_{\text{min}}} \left\{ U_i^{(t)} < 0 \right\} \right) \]

where \( \Delta_t = \log \left( \frac{\text{Odds}_L}{\text{Odds}_t} \right) \) where \( \Delta_{\text{min}} \) was set to \( \Delta_{\text{min}} = 0.61 \) for Design 1 with \( \Delta = (0.59, 1.30, 0.67, 0.00)^T \). Then, EDTR_2 and EDTR_3 should be excluded from the set of best.

We chose \( \Delta_{\text{min}} = 0.9 \) with \( \Delta = (0.93, 1.93, 0.00, 1.14, 2.66, 1.94, 0.84, 0.17)^T \). Then, EDTR_2, EDTR_4, EDTR_5, EDTR_6, and EDTR_8 should be excluded from the set of best. The power plots (Figure 3) demon-
Figure 4: Real ENGAGE SMART MCB. Upper one-sided credible intervals for the difference between each embedded DTR (EDTR) and the best embedded DTR. Intervals covering 0 indicate that the corresponding embedded DTR is not statistically significantly inferior to the best embedded DTR. Being below zero indicates inferiority compared with the best.

strate the accuracy of the predicted power estimating the required sample size.

6 Constructing a set of best embedded DTRs for the ENGAGE SMART

In this section, we apply our method to the The Adaptive Treatment for Alcohol and Cocaine Dependence (ENGAGE) SMART trial to construct a set of optimal embedded DTRs for a binary outcome. We dichotomize the log of the sum of the total number of days drinking plus the total number of days using cocaine plus a small constant 0.5 and consider a positive response to be having the outcome less than the 25th percentile. We see that the optimal embedded DTRs are embedded DTRs 1 and 2. The one with the lowest point estimate is embedded DTR 2. This suggests that MI-IOP is superior to patients' choosing their own care. Furthermore, although not statistically significant different, stage-2 NFC has a greater point estimate compared to MI-PC. The probability of response in each embedded DTR was

$$(EDTR_1, EDTR_2, EDTR_3, EDTR_4) = (0.38, 0.41, 0.19, 0.22).$$

The actual power is approximately 57% for a sample size of 148, the actual sample size in the SMART. To achieve a power of 80% would require a sample size of approximately 250 subjects and for 90%, approximately
350 subjects. The proposed MCB analysis demonstrates that the embedded DTR for which there is no further care are not statistically distinguishable from the embedded DTR for which patient choice is offered in stage 2. Therefore, clinicians may choose from the set of best either embedded DTR considering other factors such as costs, treatment burden and patients preference.

7 Input parameters for sample size calculation

The input parameters are the final response rates for each embedded treatment sequence $\theta_k$ for $k = 1, ..., K$, and the stage-1 treatment response probabilities $\lambda_{A_1}$ for $A_1 \in \{-1, +1\}$. For the treatment sequences in which patients responded to the first stage treatment (probability $\lambda_{A_1}$) when continuing initial treatment, the response rate from non-SMART studies may be used. For sequences involving two sequential treatments, the response rates of the second stage treatment will yield a conservative estimate of the power, so in the absence of data on a particular sequence of treatments, one may choose the response rate of the second stage treatment obtained from existing literature. Furthermore, one may equate different branch response probabilities essentially making the assumption of no interaction between stage-1 treatment and the response rate for a particular stage-2 treatment. This may be reasonable for a SMART in which both branches have the same treatment options in stage 2. As an alternative, one may conduct a pilot SMART to estimate the response rates (Artman et al. 2018; Rose et al. 2019).
8 Discussion

An important goal of SMARTs is the determination of the best embedded DTRs. Subjects with substance use disorders are heterogeneous in their response to outcome. The optimal embedded DTRs for the ENGAGE study were those which consisted of the intensive out patient programs. Previous work has focused on inference for simple comparisons such as those between two embedded DTRs. Furthermore, methods which are applicable to more complex comparisons such as determination of the optimal embedded DTR while taking into account uncertainty has focused on continuous outcomes in the frequentist setting. We made two main contributions. First, we extended existing methodologies from continuous to binary outcomes and from the frequentist to the Bayesian setting. In particular, we applied the algorithm in Mandel & Betensky (2008) to MCB to construct a set of optimal embedded DTRs. Secondly, we provide a means for sample size calculations without the need for knowledge of the covariance matrix of log-odds ratios and without normality assumptions.

We proved the validity of our method and demonstrated its application on real data, the ENGAGE SMART. Recently, there has been work to develop sample size formula based off Q-learning for a continuous outcome in Rose et al. (2019). It would be of interest to extend the proposed Bayesian MCB framework to Q-learning with binary outcomes. Furthermore, it would be valuable to extend MCB to constructing a set of best for longitudinal outcomes or zero-inflated outcomes. It would be straightforward to extend the Bayesian approach to encompass continuous outcomes.

References

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

Artman, W.J., Nahum-Shani, I., Wu, T., Mckay, J.R., & Ertefaie, A. 2018. Power analysis in a SMART design: sample size estimation for determining the best embedded dynamic treatment regime. *Biostatistics.*

Black, J.J, & Chung, T. 2014. Mechanisms of change in adolescent substance use treatment: How does treatment work? *Substance abuse, 35*(4), 344–351.

Chakraborty, B, & Moodie, E.E. 2013. *Statistical methods for dynamic treatment regimes.* Springer, New York.
Chakraborty, B, & Murphy, S.A. 2014. Dynamic treatment regimes. *Annual review of statistics and its application*, 1(1), 447–464.

Crivello, A.I., Levy, J.A., & Murphy, S.A. 2007a. *Evaluation of Sample Size Formulae for Developing Adaptive Treatment Strategies Using a SMART Design*. Tech. rept. No. 07-81. University Park, PA: The Pennsylvania State University, The Methodology Center.

Crivello, A.I., Levy, J.A., & Murphy, S.A. 2007b. *Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies*. Tech. rept. No. 07-82. University Park, PA: The Pennsylvania State University, The Methodology Center.

Dziak, J.J, Yap, J.R.T, Almirall, D, McKay, J.R., Lynch, K.G., & Nahum-Shani, Inbal. 2019. A Data Analysis Method for Using Longitudinal Binary Outcome Data from a SMART to Compare Adaptive Interventions. *Multivariate behavioral research*, 1–24.

Ertefaie, A, Wu, T, Lynch, K.G., & Nahum-Shani, I. 2015. Identifying a set that contains the best dynamic treatment regimes. *Biostatistics*, 17(1), 135–148.

Hsu, J.C. 1981. Simultaneous confidence intervals for all distances from the “best”. *The Annals of Statistics*, 9(5), 1026–1034.

Hsu, J.C. 1984. Constrained Simultaneous Confidence Intervals for Multiple Comparisons with the Best. *Ann. Statist.*, 12(3), 1136–1144.

Hsu, J.C. 1996. *Multiple Comparisons: Theory and Methods*. CRC Press, London.

Kidwell, K.M., Seewald, N.J., Tran, Q, Kasari, C, & Almirall, D. 2018. Design and analysis considerations for comparing dynamic treatment regimens with binary outcomes from sequential multiple assignment randomized trials. *Journal of applied statistics*, 45(9), 1628–1651.

Kranzler, H.R., & McKay, J.R. 2012. Personalized treatment of alcohol dependence. *Current psychiatry reports*, 14(5), 486–493.

Laber, E.B., Lizotte, D.J., Qian, M, Pelham, W.E., & Murphy, S.A. 2014. Dynamic treatment regimes: Technical challenges and applications. *Electronic journal of statistics*, 8(1), 1225–1272.

Lavori, P.W., Dawson, R, & Rush, A.J. 2000. Flexible treatment strategies in chronic disease: clinical and research implications. *Biological Psychiatry*, 48(6), 605–614.

Lei, H, Nahum-Shani, I, Lynch, K.G., Oslin, D, & Murphy, S.A. 2012. A SMART design for building individualized treatment sequences. *Annual Review of Clinical Psychology*, 8(1), 21–48.
Mandel, M, & Betensky, R A. 2008. Simultaneous confidence intervals based on the percentile bootstrap approach. *Computational statistics & data analysis*, 52(4), 2158–2165.

McKay, James R. 2009. Continuing care research: What we have learned and where we are going. *Journal of substance abuse treatment*, 36(2), 131–145.

McKay, J.R, Drapkin, M.L., Van Horn, D.H.A, Lynch, K.G., Oslin, D.W., DePhilippis, D, Ivey, M, & Cacciola, J.S. 2015. Effect of patient choice in an adaptive sequential randomization trial of treatment for alcohol and cocaine dependence. *Journal of consulting and clinical psychology*, 83(6), 1021.

Murphy, S.A. 2003. Optimal dynamic treatment regimes. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 65(2), 331–355.

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

Murphy, S.A., van der Laan, M.J., Robins, J.M., & Group, Conduct Problems Prevention Research. 2001. Marginal mean models for dynamic regimes. *Journal of the American Statistical Association*, 96(456), 1410–1423.

Nahum-Shani, I, Qian, M, Almirall, D, Pelham, W.E., Gnagy, B, Fabiano, G.A., Waxmonsky, J.G., Yu, J, & Murphy, S.A. 2012. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological methods*, 17(4), 457–477.

Ogbagaber, S.B., Karp, J, & Wahed, A.S. 2016. Design of sequentially randomized trials for testing adaptive treatment strategies. *Statistics in medicine*, 35(6), 840–858.

Robins, James. 1986. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical modelling*, 7(9-12), 1393–1512.

Robins, J.M. 2004. Optimal structural nested models for optimal sequential decisions. Pages 189–326 of: Optimal structural nested models for optimal sequential decisions. Proceedings of the second seattle Symposium in Biostatistics. Springer.

Rose, E.J., Laber, E.B., Davidian, M, Tsiatis, A.A, Zhao, Y.Q., & Kosorok, M.R. 2019. Sample Size Calculations for SMARTs. *arXiv preprint arXiv:1906.06646*.
Van Horn, D.H.A, Drapkin, M, Lynch, K.G., Rennert, L, Goodman, J.D., Thomas, T, Ivey, M, & McKay, J.R. 2015. Treatment choices and subsequent attendance by substance-dependent patients who disengage from intensive outpatient treatment. *Addiction research & theory*, 23(5), 391–403.

Witkiewitz, K, Finney, J.W., Harris, A.H.S, Kivlahan, D.R., & Kranzler, H.R. 2015. Recommendations for the design and analysis of treatment trials for alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, 39(9), 1557–1570.

Yan, Xiaoxi, Ghosh, Palash, & Chakraborty, Bibhas. 2020. Sample size calculation based on precision for pilot sequential multiple assignment randomized trial (SMART). *Biometrical Journal*. 
A Proofs

A.1 Robin’s G-Computation formula

\[
\begin{align*}
\Pr(Y^{(l)} = 1) &= \Pr(Y = 1 \mid A_1, \text{EDTR}^{(l)}) \\
&= \Pr(Y = 1 \mid A_1, S = 1, \text{EDTR}^{(l)}) \Pr(S = 1 \mid A_1, \text{EDTR}^{(l)}) \\
&\quad + \Pr(Y = 1 \mid A_1, S = 0, \text{EDTR}^{(l)}) \Pr(S = 0 \mid A_1, \text{EDTR}^{(l)}) \\
&= \Pr(Y = 1 \mid A_1, S = 1) \Pr(S = 1 \mid A_1) + \Pr(Y = 1 \mid A_1, S = 0, \text{ANR}^2) \Pr(S = 0 \mid A_1)
\end{align*}
\]

A.2 Proof of credible interval coverage

We wish to construct simultaneous $100(1 - \alpha)\%$ one-sided upper credible intervals for $\zeta^{(l)}$, $l = 1, \ldots, L$.

Denote the upper limit for the $l$th embedded DTR by $U^{(l)}$. Then, $U^{(l)}$ satisfies

\[
\Pr\left(\bigcap_{l=1}^{L} \{\zeta^{(l)} \leq U^{(l)}\}\right) = 1 - \alpha.
\]

This is equivalent to

\[
M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{\zeta^{(l)}_{m,l} \leq U^{(l)}\}\right) = M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{\zeta^{(l)}_{r(m,l),l} \leq U^{(l)}\}\right)
\]

\[
M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{\zeta^{(l)}_{r(m,l),l} \leq U^{(l)}\}\right) \to 1 - \alpha \text{ as } M \to \infty.
\]

Let $U^{(l)} = s_{(r_{1 - \alpha})}^{(l)}$ where $r_{1 - \alpha}$ is the $1 - \alpha$ quantile of $r(1), \ldots, r(M)$ where $r(m) = \max_l r(m, l)$. Then,

\[
M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{\zeta^{(l)}_{r(m,l),l} \leq U^{(l)}\}\right) = M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{\zeta^{(l)}_{r(m,l),l} \leq \zeta^{(l)}_{r_{1 - \alpha}}\}\right)
\]

\[
= M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\bigcap_{l=1}^{L} \{r(m,l) \leq r_{1 - \alpha}\}\right)
\]

\[
= M^{-1} \sum_{m=1}^{M} \mathcal{I}\left(\max_l r(m,l) \leq r_{1 - \alpha}\right)
\]

\[
= M^{-1} \sum_{m=1}^{M} \mathcal{I}\{r(m) \leq r_{1 - \alpha}\} \to 1 - \alpha.
\]

QED.