Comparing Dynamic Treatment Regimes Using Repeated-Measures Outcomes: Modeling Considerations in SMART Studies

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Abstract

A dynamic treatment regimen (DTR) is a sequence of decision rules, each of which recommends a treatment based on a patient’s past and current health status. Sequential, multiple assignment, randomized trials (SMARTs) are multi-stage trial designs that yield data specifically for building effective DTRs. Modeling the marginal mean trajectories of a repeated-measures outcome arising from a SMART presents challenges, because traditional longitudinal models used for randomized clinical trials do not take into account specific design features of SMART. We discuss modeling considerations, emphasizing the importance of considering the timing of repeated measures in relation to the treatment stages in a SMART. For illustration, we use data from three SMART case studies with increasing level of complexity, in autism, child attention deficit hyperactivity disorder (ADHD), and adult alcoholism. In the autism SMART, the duration of stage one was the same for all participants. In the ADHD SMART, the duration of stage one varied among participants and was determined by the participant’s response to the initial treatment. In the alcoholism SMART, the duration of stage one also varied among participants, with non-responders transitioning to stage two at any of a variety of weeks prior to week eight, whereas responders transitioned to stage two at week eight. In all three SMARTs we illustrate how to accommodate these design features along with the timing of the repeated measures when comparing DTRs based on marginal mean trajectories.
I. INTRODUCTION

A dynamic treatment regimen (DTR) (Robins, 1986, 1989, 1993, 1997, 2004) is a sequence of decision rules, each taking the current characteristics and past treatments of a patient as input, and outputting a recommended treatment. Also known as adaptive treatment strategies (Lavori and Dawson, 2000, 2008; Murphy, 2005; Thall et al., 2000, 2002), treatment policies (Lunceford et al., 2002; Wahed and Tsiatis, 2004, 2006) or adaptive interventions, dynamic treatment regimens aim to provide treatments/interventions only when patients need them, and adapt the type or dosage of treatments/interventions to patients’ changing needs. DTRs are particularly useful for the treatment of chronic diseases, where the status of the individual is often waxing and waning status, or in settings in which no one treatment is effective for most individuals, and thus a sequence of treatments that are adapted to the patients’ needs and conditions are often needed to achieve an improvement in health. An example DTR for improving spoken communication in children with autism spectrum disorder (Tager-Flusberg and Kasari, 2013; Kasari et al., 2014) is “Begin with a therapist-delivered behavioral language intervention (BLI) for 12 weeks. At the end of week 12, if a child is a slow responder, augment BLI with an augmentative or alternative communication (AAC) approach, most often a speech-generating device; otherwise, if the child shows early signs of response, continue with the first stage BLI for an additional 12 weeks.”

A vast literature is available on the methodology that can be used to inform the construction of effective DTRs with both observational data and experimental data. These methods include marginal structural models (Orellana et al., 2006; van der Laan, 2006; Robins et al., 2008; Bembom and van der Laan, 2008; Orellana et al., 2010), inverse probability weighting (Zhang et al., 2013), structural nested mean models (Robins, 2004; Moodie et al., 2007), likelihood-based methods (Chaffee and van der Laan, 2012), and statistical learning-based methods (Zhao et al., 2014).

This manuscript focuses on statistical methods for comparing DTRs on the basis of a
repeated-measures outcome observed across the multiple stages of treatment in a sequential, multiple assignment, randomized trial (SMART; Lavori and Dawson (2000, 2004); Murphy (2005)). In the context of the autism example, a researcher may be interested in comparing two DTRs, say, based on the trajectory of the number of socially communicative utterances collected at baseline and weeks 12, 24 and 36. Study features that are unique to SMARTs make repeated-measures modeling a challenge. In this setting, repeated-measures models must account appropriately for (i) the temporal ordering of treatments relative to outcome measurement occasions and (ii) the fact that participants may transition from one stage of treatment to the next at different time points. In this manuscript we discuss how to accommodate SMART design features in modeling repeated-measures outcomes. For illustration, we use data from three SMART case studies in autism, child attention deficit hyperactivity disorder (ADHD), and adult alcohol dependence. Each case study presents a progressively more complex SMART design. We generalize the weighted-and-replicated methods of Orellana and colleagues (Orellana et al., 2006; Robins et al., 2008; Orellana et al., 2010) to estimate the parameters in our repeated-measures models.

This technical report is organized as follows. In Section 2, we describe SMART studies in more detail. In Section 3, we present and discuss general principles for modeling the repeated-measures outcomes in SMART and illustrate these principles with the three SMART studies. A weighted-and-replicated estimator for the parameters in the repeated-measures marginal model is proposed in Section 4. In Section 5 we present the data analysis results for the three SMART studies. In Section 6 we report results of simulation studies illustrating the importance of modeling considerations. Finally, a discussion, including other possible ideas for modeling repeated-measures outcomes from a SMART, is presented in Section 7.
II. SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIALS

In a SMART participants proceed through multiple treatment stages, and at each treatment stage the participant may be randomized to one of several treatment options available at that stage. Often, subsequent randomized treatment options in a SMART are restricted depending on response to prior treatment. A variety of these trials have been conducted, with some of the earliest taking place in cancer research, for the purpose of developing medication algorithms for leukemia (Thall et al., 2002), or to develop adaptive treatment of prostate cancer (Thall et al., 2000). A selection of SMART studies may be found at http://methodology.psu.edu/ra/adap-inter/projects.

Below we present the three SMART studies that we analyze in this paper: the autism, ADHD and ExTENd studies. These designs vary in complexity, with the autism study being the least complex and ExTENd being the most complex of the three. The complexity in study design is in terms of the re-randomization scheme and the number of time points at which participants can be re-randomized.

Figure 1 provides the design of the autism SMART (C. Kasari, P.I.; Kasari et al. (2014)), for the treatment of minimally verbal children with autism, aged 5 to 8 years. In this SMART, at the first stage children were randomized to BLI or BLI+AAC. This stage lasted for 12 weeks for all children. After 12 weeks, children were classified as either early responders or slow responders and made the transition to the second stage. In the second stage, early responders continued with the interventions that were assigned in the first stage; slow responders to initial BLI+AAC received intensified BLI+AAC (more sessions per week), and slow responders to initial BLI were randomly assigned either to receive intensified BLI (more sessions per week) or to be augmented to BLI+AAC. The second stage treatment lasted for 12 weeks.

SMARTs, such as the one shown in Figure 1, have a set of DTRs embedded within them. In this SMART there are three embedded two-stage DTRs; they are listed in Table I. Note that some participants in a SMART had treatment sequences that are consistent with
FIG. 1. An example SMART for the development of a DTR for children with autism who are minimally verbal. R = randomization. BLI = behavioral language intervention. AAC = augmentative or alternative communication approach.

more than one DTR; in other words, those participants received treatment sequences that would be assigned under more than one DTR. For example, early responders to BLI have a treatment sequence that is consistent with both DTR#1 and DTR#2.

Figure 2 shows the design of the ADHD SMART for the treatment of children (aged 5 to 13 years with mean of 8 years) with ADHD (W. Pelham, P.I.). In this SMART, at the first stage children were randomly assigned to begin with low-intensity behavioral modification (BMOD) or with low-dose medication (MED; methylphenidate). Starting at the end of month two, children were assessed monthly for response/non-response to the initial
intervention. See Lei et al. (2012) and Nahum-Shani et al. (2012) for more details concerning the definition of response/non-response. Children who met the criteria for non-response were immediately re-randomized to either an intensified version of the initial intervention (INT) or to augmenting the initial intervention with the alternative intervention (MED+BMOD). Children who continued to respond remained on their initial treatment. Treatment duration was eight months in total for all children in the study.

![Diagram of SMART for ADHD development](image)

**FIG. 2.** An example SMART for the development of a DTR for children with attention deficit/hyperactivity disorder. R = randomization. MED = medication. BMOD = behavioral modification.

The ADHD SMART differs from the autism SMART in that the duration of stage one varied among participants. Those who met the non-response criteria at later time points
would transition to the second treatment stage later in the study period, and this was determined by how participants responded to the initial treatment. Those who continued to respond to the initial treatment would not experience a transition to the second stage. The ADHD SMART has four embedded DTRs, as a result of the initial randomization and re-randomization for non-responders.

Figure 3 shows the design of a third SMART study, the ExTENd SMART designed for individuals with alcohol dependence. At the entry of this study, patients were randomized to either a stringent definition of early non-response (two or more heavy drinking days within the first eight weeks) or a lenient definition of early non-response (five or more heavy drinking days within the first eight weeks). All patients received open-label Naltrexone (NTX; medication, an opiate antagonist) as the initial treatment. Starting at the end of week two, patients were assessed weekly for response/non-response to the initial intervention; those who met the criterion for early non-response immediately transitioned to the second stage and were re-randomized to either NTX+CBI or Placebo+CBI, where CBI stands for combined behavioral interventions. Patients who did not meet their assigned non-response criterion by week eight were classified as responders and were re-randomized to either usual care (UC) or telephone disease management (TDM). The second-stage treatment lasted four months.

The ExTENd SMART design is more complex than the autism and ADHD studies. Both responders and non-responders to the initial treatment were re-randomized to subsequent treatment options. The duration of stage one varied among participants: non-responders transitioned to stage two at any of a variety of weeks prior to week eight whereas all responders transitioned to stage two at week eight. The ExTENd SMART has eight embedded DTRs, as a result of the initial randomization and re-randomization of both responders and non-responders.
FIG. 3. An example SMART for the development of a DTR for adults with alcohol dependence. \( R \) = randomization. \( NTX \) = Naltrexone. \( TDM \) = telephone disease management. \( UC \) = usual care. \( CBI \) = combined behavioral interventions. \( MM \) = medical management.

III. REPEATED-MEASURES MARGINAL MODEL

In this section we develop marginal models for comparing the embedded DTRs in a SMART based on repeated measures. For simplicity, we focus on two-stage SMARTs; all ideas can be extended readily to SMARTs with more than two stages. We label each embedded DTR in a SMART by the pair \((a_1, a_2)\), where \( a_j \) is used to denote a treatment option at stage \( j \). For example, in the autism SMART, we let \( a_1 = 1 \) denote BLI and let
\[ a_1 = -1 \] denote BLI+AAC. We let \( a_2 = 1 \) denote assigning intensified BLI to slow responders to first stage BLI and let \( a_2 = -1 \) denote assigning BLI+AAC to slow responders to first stage BLI. Note that in the autism SMART, \( a_2 \) is nested within \( a_1 = 1 \) because only slow responders to BLI were re-randomized. See Table I for the labels of all three embedded DTRs in the autism study.

\( X \) denotes baseline, pre-randomization covariates, such as age, gender and ethnicity. In all models below, the variables in \( X \) are mean-centered to facilitate model interpretations. \( Y_t \) denotes the repeated-measures primary outcome that is of scientific interest, observed at time \( t, t \in T \). In the autism study, \( Y_t \) is the number of socially communicative utterances at week \( t = 0 \) (baseline), 12, 24, 36. For this outcome, higher values of \( Y_t \) are more favorable.

\[ E_{(a_1,a_2)}[Y_t | X] \] is the marginal mean of the repeated-measures outcome \( Y_t \) under the embedded DTR defined by \((a_1, a_2)\), conditional on baseline \( X \). The primary focus of this manuscript is on developing parametric models \( \mu_t(a_1, a_2, X; \beta) \) for \( E_{(a_1,a_2)}[Y_t | X] \) under a variety of different SMART designs. We also discuss the estimation of the unknown parameter \( \beta \).

A. A Traditional Approach to Modeling Repeated Measures in a SMART

To appreciate the need to consider the specific features of a SMART design in repeated-measures modeling, we first consider using a traditional approach to comparing the mean trajectories between two DTRs in the autism SMART. For simplicity, suppose we compare DTR#1 (labeled (1, -1) in Table I) versus DTR#2 (labeled (1, 1) in Table I) using only data from children who began with BLI \((a_1 = 1)\). A traditional model in this case might be

\[ E_{(a_1,a_2)}[Y_t | X] = \eta^T X + \beta_0 + \beta_1 t + \beta_2 1_{a_1=1,a_2=1} t. \]

In this model, the trajectories associated with the two DTRs are modeled as two straight lines that start with the same intercept at \( t = 0 \): the marginal mean of \( Y_t \) under DTR \((1, -1)\) is \((\beta_0 + \beta_1 t)\), whereas the marginal mean of \( Y_t \) under DTR \((1, 1)\) is \((\beta_0 + (\beta_1 + \beta_2) t)\). In this example of a traditional approach, therefore, the difference between the marginal
mean trajectories is given by the single parameter $\beta_2$. This model will incur bias if either one of the two DTRs does not have a linear mean trajectory. However, in a study such as the autism SMART, it may be important to accommodate a possible deflection at week 12 in the mean trajectory because this is the point at which slow responders switch to a different treatment. Further, since neither participants nor staff were aware of the randomly assigned second-stage treatment during the first stage of treatment (this is a typical feature of SMART designs), these two DTRs should not differ, on average, from $t = 0$ to $t = 12$. In Section VI we investigate, via simulations, the bias that occurs when adopting a traditional slope or quadratic model to analyze repeated measures from a SMART. An example of an improved model is presented in the next section.

In addition, when it is no longer reasonable to adopt simple models such as the slope model above, the comparison among DTRs cannot be achieved by obtaining simple summaries, such as the ones based on $\beta$ in the above model. Thus there is a need to focus on alternative estimands to compare the DTRs based on a repeated-measures model. In the following subsections, we discuss (a) modeling considerations for $\mu_t(a_1, a_2; X; \beta)$ that are specific to SMART designs, and (b) different options for estimands in the comparison of the embedded DTRs in a SMART.

**B. Repeated-Measures Modeling Considerations: The Autism Example**

As noted earlier, modeling of a repeated-measures outcome arising from a SMART should be guided by two key principles: (a) properly accommodate the timing of repeated measures in relation to the treatment stages in a SMART; and (b) properly accommodate the restrictions applied on the randomizations by design. The autism SMART provides a relatively simple example to illustrate these modeling principles.

In the autism SMART, all participants had the same duration of stage one treatment (12 weeks) and stage two treatment (12 weeks), and they all advanced to stage two after week 12. Additionally, only slow responders to BLI were re-randomized.
The primary outcome, socially communicative utterances, was measured on four occasions. Baseline measurement $Y_0$ was pre-treatment; $Y_{12}$ was right before the second treatment stage (re-randomization, if applicable, happened right after $Y_{12}$); both $Y_{24}$ and $Y_{36}$ were post entry to the second treatment stage. Since all participants transitioned at $t = 12$, one approach to modeling the repeated measures in the autism SMART is using a continuous, piecewise marginal model with a knot at week 12. For example, consider the following marginal model for $Y_t$:

$$E_{(a_1,a_2)}[Y_t|X] = \eta^T X + \beta_0 + 1_{t \leq 12}\{\beta_1 t + \beta_2 t a_1\} + 1_{t > 12}\{12\beta_1 + 12\beta_2 a_1 + \beta_3(t - 12) + \beta_4(t - 12)a_1 + \beta_5(t - 12)1_{a_1=1}a_2\},$$

(1)

where the unknown parameters $\beta = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$ model the effect of the embedded DTRs over time; and $\eta$ captures the association between the time-varying outcome and mean-centered baseline covariates $X$; $\beta$ will be of primary interest.

This example model entails two restrictions. The first restriction is that $Y_0$ is modeled to have the same marginal mean for all three embedded DTRs. This is a common restriction used in the analysis of longitudinal randomized trials (Liang and Zeger, 2000) since, by design, treatment groups are not expected to differ at baseline (prior to randomization). The second restriction is that the marginal mean trajectory is assumed to be the same between embedded DTRs (1, 1) and (1, -1) until week 12. This restriction is unique to SMARTs. It is consistent with the study design, in that (1) these two DTRs are identical up to week 12 and (2) re-randomization to second stage treatment does not occur until week 12 (i.e., there can be no expectancy or anticipatory effects due to knowledge of second stage treatments during stage one).

For simplicity, the example model above assumes a piecewise linear trend. In practice, a quadratic mean trajectory (or some other trend) may be more appropriate.
C. Repeated-Measures Modeling Considerations: The ADHD Example

In analyzing the ADHD SMART, we focus on comparing the four embedded DTRs based on repeated measures of school performance measured on eight occasions – at the end of each month of the study (i.e., \(Y_1, ..., Y_8\)). Note that unlike in the autism SMART, this repeated-measures outcome is unavailable at baseline. This outcome is coded so that higher values are more favorable. Each of the four embedded DTRs is labeled by a pair \((a_1, a_2)\). Let \(a_1 = 1\) denote starting with low-intensity BMOD and let \(a_1 = -1\) denote starting with low-dose MED. Let \(a_2 = 1\) denote intensifying the initial treatment for slow responders and let \(a_2 = -1\) denote augmenting the initial treatment with the alternative treatment for slow responders.

As discussed previously, the SMART design in the ADHD study is more complex relative to the autism study. While the duration of the entire study was the same for all participants (i.e., eight months), the duration of the first and the second treatment stages varied across participants. More specifically, the duration of the first treatment stage could be as short as two months (for the children who became non-responders at the end of month two), or as long as eight months (for the children who continued to respond throughout the entire study). This has implications for modeling the marginal mean under a DTR in that, for a fixed \(t > 2\), the marginal mean of \(Y_t\) is a weighted average of the mean for participants who have transitioned and the mean for participants who have yet to transition; as a result, there may be deflections in the marginal mean from as early as \(t = 2\) to as late as \(t = 7\).

Additionally, the initial treatment (BMOD versus MED) had an impact on participants’ performance, which determined whether or when the participants transitioned to the second stage as non-responders. In particular, among the 75 participants who were assigned to MED initially, only 19 transitioned to stage two (as slow responders) at month two; on the contrary, among the 75 participants who were assigned to BMOD initially, 36 transitioned to stage two (as slow responders) at month two. Therefore, we may allow the DTRs that start with BMOD to have a pattern of deflection in the marginal mean different from that
of DTRs that start with MED (see the exploratory plot in the online appendix).

Based on the discussions above, we propose to model the repeated measures from the ADHD study as shown below:

\[
E_{(a_1,a_2)}[Y_t|X] = \eta^T X + \beta_0 + \beta_1 a_1 + 1_{a_1=1}1_{t \leq 2} \beta_2 (t-1) \\
+ 1_{a_1=1}1_{t > 2} (\beta_2 + 1_{a_2=1} (\beta_3 (t-2) + \beta_4 (t-2)^2) + 1_{a_2=-1} \beta_5 (t-2)) \\
+ 1_{a_1=-1}1_{t \leq 3} \beta_6 (t-1) \\
+ 1_{a_1=-1}1_{t > 3} (2 \beta_6 + 1_{a_2=1} \beta_7 (t-3) + 1_{a_2=-1} \beta_8 (t-3)).
\]

Here, the DTR (BMOD, BMOD+MED) (i.e., \((a_1, a_2) = (1, -1)\)) is assumed to have a piecewise linear trajectory with a knot at \(t = 2\), whereas (BMOD, INT) (i.e., \((a_1, a_2) = (1, 1)\)) has the same mean trajectory as (BMOD, BMOD+MED) until \(t = 2\) and then develops a quadratic trajectory. The two DTRs that begin with MED are assumed to have piecewise linear trajectories with a knot at \(t = 3\) and they share the same mean trajectory until \(t = 3\).

D. Repeated-Measures Modeling Considerations: The ExTENd Example

The greater complexity in the ExTENd SMART necessitates more careful modeling considerations. In analyzing the ExTENd SMART, we focus on comparing the eight embedded DTRs based on a repeated-measures outcome of alcohol craving collected on 17 occasions: at baseline \((Y_0)\) and the end of each week for 16 weeks \((Y_1, ..., Y_{16})\). This outcome is recoded so that higher values are more favorable. Because all participants were randomized at study entry and both responders and non-responders were re-randomized to second-stage treatment options, there are eight embedded DTRs in total. The eight DTRs are denoted by \((a_1, a_{2R}, a_{2NR})\), where \(a_1\) is used to denote whether the stringent definition or the lenient definition of early non-response is adopted, \(a_{2R}\) is used to denote a treatment option for responders at stage two, and \(a_{2NR}\) is used to denote a treatment option for non-responders at stage two.

For all participants, the transition time to the second treatment stage ranged from the end of week two to the end of week eight. As a result, similar to the ADHD study, for a
fixed, $Y_t$ may come from different treatment stages for different participants. In addition, note that DTRs that begin with the same $a_1$ might differ only in $a_{2R}$ (how responders are treated in the second stage), only in $a_{2NR}$ (how non-responders are treated in the second stage), or both. The impact of differing $a_{2NR}$ can take place from the end of week two (non-responders could start to transition to stage two as early as the end of week two); however the impact of differing $a_{2R}$ can only take place from the end of week eight (responders could only transition to stage two at the end of week eight).

Because of the complications illustrated above, and given the relatively frequent repeated measures, we do not model each of the mean trajectories parametrically; instead, we adopt flexible spline-based models with constraints that are consistent with our previous discussions. First, we allow two DTRs that differ only in $a_{2NR}$ to start to differ in the mean trajectories after $t = 2$, because participants could become non-responders and, therefore, receive salvage treatment options specified by $a_{2NR}$ on or after week two. Second, we allow two DTRs that differ only in $a_{2R}$ to start to differ in the mean trajectories after $t = 8$, because on week eight participants could become responders and, therefore, receive the maintenance treatment options specified by $a_{2R}$. Aside from forcing all DTRs to have the same mean of $Y_0$ and these two constraints, we allow the trajectories of the DTRs to be regression splines. In Appendix C we provide more details about incorporating these concerns into the regression splines model.

E. Estimands

In repeated-measures analysis of SMARTs, a variety of interesting estimands are possible for the comparisons among embedded DTRs. Here, we present two that are clinically important and easy to communicate: change score comparisons and area under curve (AUC). The first approach, change score comparisons, measures the differences among embedded DTRs in terms of change in response from $t_1$ to $t_2$. A change score estimand is
\[ \Delta_{t_1,t_2} = E_{(a_1,a_2)}[Y_{t_2} - Y_{t_1}] - E_{(a_1^*,a_2^*)}[Y_{t_2} - Y_{t_1}], \]
where \((a_1, a_2)\) and \((a_1^*, a_2^*)\) are two embedded DTRs. In the autism example, a change score comparison from week 0 to week 36 compares the embedded DTRs in terms of the mean increase from baseline to the end of follow-up in the number of socially communicative utterances.

The second approach, AUC, summarizes the cumulative amount of \(Y_t\) within a time range \((t_1, t_2)\); it provides an alternative single number summary of the overall mean trajectory under each embedded DTR. In the autism study, the AUC of \(Y_t\) from \(t = 0\) to \(t = 36\) for a specific embedded DTR has a clinically relevant interpretation as the average total number of socially communicative utterances from \(t = 0\) to \(t = 36\) under this DTR.

Certainly, the AUC is a more informative summary of the marginal mean trajectory than the change score, because AUC captures not only change from the start to the end point, but also captures characteristics of the progression in the mean outcome during the period. Thus in the data analysis we report the AUC for the embedded DTRs.

## IV. ESTIMATOR FOR REPEATED-MEASURES MARGINAL MODEL

### A. Observed Data

For simplicity, we present the proposed estimator for the repeated-measures marginal model with the autism example. Details about how this estimator is implemented to analyze the ADHD and ExTENd SMARTs can be found in Appendix B and Appendix C.

The structure of the data is as follows. For individual \(i\) \((i = 1, ..., N)\), we observe \(X_i, A_{1,i}, R_i, A_{2,i}\) and \(Y_{t,i}, t \in T\). \(X\) includes a set of mean-centered baseline covariates; \(A_1\) denotes the first-stage treatment to which an individual is randomized; \(R\) is the indicator of early response; \(A_2\) denotes the second-stage treatment to which the individual is re-randomized. \(Y_t\) is the observed value of the longitudinal outcome at time \(t\).

For example, in the autism SMART, we have \((X_i, Y_{0,i}, A_{1,i}, Y_{12,i}, R_i, A_{2,i}, Y_{24,i}, Y_{36,i})\). \(A_{1,i}\) denotes whether the child was randomized to BLI \((A_{1,i} = 1)\) or BLI+AAC \((A_{1,i} = -1)\) during the first 12 weeks. For slow responders to BLI \((A_{1,i} = 1, R_i = 0)\), \(A_{2,i}\) denotes whether the
child was re-randomized to intensified BLI ($A_{2,i} = 1$) or BLI+AAC ($A_{2,i} = -1$).

B. A Review of the Weighted-and-Replicated Estimator

This section is a review of a weighted-and-replicated (WR) estimator for comparing the DTRs with respect to an end-of-study outcome (Orellana et al., 2006; van der Laan, 2006; Robins et al., 2008; Orellana et al., 2010; Nahum-Shani et al., 2012), illustrated with the autism example. In the following section, we extend this estimator to longitudinal outcomes.

Suppose that one is interested in comparing the mean of $Y_{36}$ among the embedded DTRs, and assume that $\mu_{36}(a_1, a_2, X; \beta)$ is a parametric model for the marginal mean of $Y_{36}$ under embedded DTR $(a_1, a_2)$, which takes a linear form in $\beta$ and has derivative $d(a_1, a_2, X)$ with respect to $\beta$. The WR estimator for $\beta$ is obtained by solving the following estimating equation:

$$0 = \sum_{i=1}^{N} \sum_{(a_1, a_2)} I\{\text{treatment sequence of individual } i \text{ consistent with DTR } (a_1, a_2)\}$$

$$\quad \cdot d(X_i, a_1, a_2) W_i (Y_{36,i} - \mu_{36}(X_i, a_1, a_2; \beta)),$$

where $I\{\text{treatment sequence of individual } i \text{ consistent with DTR } (a_1, a_2)\}$ is a binary indicator that the individual $i$ was assigned to treatments that would be observed under the DTR $(a_1, a_2)$; and $W$ is the product over stage-specific weights, each being the inverse probability of receiving the observed treatment, conditional on the observed covariate and treatment history. In a SMART, $W$ is known, by design. For example in the autism study, $W = 1/(Pr(A_1|X, Y_0) \cdot Pr(A_2|X, Y_0, A_1, Y_{12}, R))$. Slow responders to BLI receive a weight equal to 4; all the other participants receive a weight equal to 2.

To appreciate why weighting is necessary, note that by design, BLI slow responders are randomized twice, whereas other participants are randomized only once; thus, slow responders to BLI would have a 1/4 chance of following the sequence of treatments they were offered, whereas other participants would have a 1/2 chance of following the treatments they were offered. Therefore, slow responders to BLI are under-represented in the data. To
account for this imbalance, weights inversely proportional to the probability of being offered a particular treatment sequence are employed in the estimating equation.

Next, note that this estimating equation is an aggregate of estimating equations targeting each of the embedded DTRs. In a SMART, each individual may be consistent with one or more embedded DTRs depending on the study design. For example, in the autism SMART, responders to initial BLI are consistent with DTRs (1, 1) and (1, -1); that is, their treatment sequences are identical to the treatment sequences that would be recommended if embedded DTRs (1, 1) or (1, -1) are followed. To account for this “sharing” of observations, those observations contribute to the estimating functions for multiple DTRs.

C. An Extension for Repeated Measures

For the estimation of the repeated-measures marginal model, we propose a longitudinal version of the WR estimator reviewed above. Robins and colleagues investigated estimators to study the effect of time-varying treatment on repeated-measures outcomes (Robins (2000); Hernán et al. (2002); Robins et al. (1999)). The estimator we suggest is an extension of their work to comparisons among DTRs.

Let \( Y_i = (Y_{0,i}, Y_{1,i}, ..., Y_{T,i})^T \) denote the vector of repeated-measures outcomes for individual \( i \). Denote the vector of the model for the marginal mean as \( \mu(X_i, a_1, a_2; \beta, \eta) \), where \( \mu = (\mu_0, \mu_1, ..., \mu_T)^T \). Recall \( \mu_i(x, a_1, a_2; \beta, \eta) \) is a parametric model for the marginal mean of \( Y_i \) among participants that have pre-treatment baseline covariates equal to \( x \), under the embedded DTR labeled \( (a_1, a_2) \). Denote the derivative of \( \mu(X_i, a_1, a_2; \beta, \eta) \) with respect to \( (\eta, \beta) \) as \( D(X_i, a_1, a_2) \). \( D(X_i, a_1, a_2) \) is a \((T + 1)\)-by-\( p \) matrix, where \( p \) is the dimension of \( (\eta, \beta) \).

The proposed estimator for \( (\eta, \beta) \) for a general SMART design is

\[
0 = \sum_{i=1}^{N} \sum_{(a_1, a_2)} I\{\text{treatment sequence of individual } i \text{ consistent with DTR } (a_1, a_2)\} \\
\quad \cdot D(X_i, a_1, a_2)^T V(a_1, a_2)^{-1} W_i (Y_i - \mu(X_i, a_1, a_2; \beta, \eta)).
\]  

(3)
$V(a_1, a_2)$ is a working variance-covariance matrix of $(Y_0, Y_1, ..., Y_T)^T$ conditional on the baseline $X$, under the embedded DTR labeled $(a_1, a_2)$. The weight $W$ is used to account for the fact that participants received the observed treatment sequences with different probabilities. In the autism example, $W = 1/(Pr(A_1|X, Y_0) \cdot Pr(A_2|X, Y_0, A_1, Y_{12}, R))$. The choice of the working variance-covariance matrix $V(a_1, a_2)$ does not have an impact on the unbiasedness of the estimating equation above, given that the marginal model $\mu(X, a_1, a_2; \beta, \eta)$ and the weight $W$ are correctly specified. Asymptotics of this estimator is provided in the online appendix; in particular, the formula for the asymptotic standard error of $\hat{\beta}$ is also provided.

This proposed estimator for the repeated-measures marginal model is an extension of the WR estimator to accommodate a repeated-measures outcome. Each patient can now be conceptualized to have a vector-valued outcome. Moreover, this proposed estimator uses a working variance-covariance matrix for the vector of repeated measures, which is a strategy that is usually taken when performing longitudinal analysis, for the purpose of improving statistical efficiency (Zeger and Liang, 1986). Note that the weighting scheme here is consistent with the weighting scheme used in Robins (1998); Vansteelandt (2007), which concern the estimation of time-varying treatment effect on time-varying outcomes.

**D. Implementing the Proposed Estimator**

The proposed estimator can be conceptualized as an estimating equation based on an augmented data set, as follows:

$$0 = \sum_{j=1}^{M} D(X_j, A_{1,j}, A_{2,j})^T V(A_{1,j}, A_{2,j})^{-1} W_i(Y_j - \mu(X_j, A_{1,j}, A_{2,j}; \beta, \eta)).$$ (4)

Here, an augmented data set of size $M = N + K$ is used, with the additional rows arising from $K$ participants who are consistent with more than one embedded DTR and thus are replicated in the augmented data set. For example, in the autism study, $K$ is the number of responders to initial BLI, because responders to BLI are consistent with both DTR (1, 1) and DTR (1, -1). In the augmented data set, one copy is given the value $A_2 = 1$ and the other copy is given the value $A_2 = -1$; the two copies are identical in all the other
components. Therefore, In this augmented data set, unlike in the original data set, each observation is associated with only one embedded DTR.

The estimator, written in this form, can be readily implemented in any standard statistical software that implements GEE methodology (Zeger and Liang, 1986). Using this estimator, it is possible to take advantage of the within-person correlation in the repeated measures by specifying a non-independent working correlation structure, which potentially improves the efficiency of the estimator.

Efficiency improvements can also be attained by estimating the known weights \( W_i \), for example, using covariates thought to be correlated with the outcome (Hernán et al., 2002; Hirano et al., 2003; Brumback, 2009). We use this approach in our analyses of the three SMART studies.

V. DATA ANALYSIS

Here, we present the results of the data analysis of the three SMART studies. For all three SMARTs, prior to analysis, a sequential type of multiple imputation algorithm was used to replace missing values in the data set (Shortreed et al., 2014). This was done using the \texttt{mice} package in R (van Buuren and Groothuis-Oudshoorn, 2011). All estimates and standard errors reported are calculated using standard rules for combining identical analyses performed on each of the imputed data sets (Rubin, 2009). Data are analyzed using the approach outlined in Section IV.D, with an auto-regressive working correlation structure.

A. Analysis of the Autism SMART Data

We first present the analysis of data arising from the autism SMART \((N = 61)\). The weight at the first stage is estimated using age, gender, indicator of African American, indicator of Caucasian, number of socially communicative utterances at baseline; the weight (for slow responders to the initial BLI) at the second stage is estimated using number of socially communicative utterances at baseline and number of socially communicative
FIG. 4. Estimated mean trajectories under the embedded DTRs of the autism SMART.

utterances at week 12. Figure 4 displays a plot of the estimated marginal mean trajectories of socially communicative utterances for each of the three embedded DTRs. Estimates and standard errors for the parameters in the marginal model and comparisons between the three embedded DTRs based on the AUCs are given in Table III. To enhance interpretation we report estimates of AUC/36, which can be interpreted as the average number of socially communicative utterances over the course of the entire 36 week study.

The DTR (labeled (-1, ·)) that assigns BLI+AAC to all patients at the first stage (and intensifies BLI+AAC for slow responders) appears to outperform the other two embedded DTRs, in terms of the AUC (e.g., 95% CI of (BLI+AAC, ·) versus (BLI, INT) is (2.52,
(24.40)). Under this DTR, the average number of socially communicative utterances over the 36 week study is estimated to be 50.84 (95% CI (42.29, 59.39)), whereas it is smaller than 40 for the other two DTRs.

Interestingly, while the DTR that begins with BLI+AAC is superior in terms of AUC, it does not maintain the positive trend from week 12 to week 36 (change score = -1.91, 95% CI (-14.21, 10.39)), while the other two DTRs seem to show an average increasing trend during the same period (e.g., change score from week 12 to week 36 under (BLI, BLI+AAC) = 9.76, 95% CI (-6.89, 26.42)). These findings suggest that, in a study where the participants are followed for a longer period, the DTR that starts with BLI+AAC might be less advantageous than the other two DTRs; an additional study with a longer follow-up period would be needed to confirm this hypothesis.

B. Analysis of the ADHD SMART Data

Analysis of the ADHD SMART data (N = 150) is based on the marginal mean model proposed in (2). The repeated-measures outcome is the classroom performance rated by teachers; higher values indicate better classroom performance. The weight at the first stage is estimated using age, indicator of being previously medicated at home, indicator of being diagnosed with oppositional defiant disorder (ODD), baseline ADHD severity of symptoms, classroom performance rating at baseline; the weight (for non-responders) at the second stage is estimated using age, stage one treatment, time to re-randomization, classroom performance rating at baseline and immediately prior to re-randomization.

Table IV presents the estimated AUCs for the four embedded DTRs and their comparisons. AUC/7 can now be interpreted as the average classroom performance rating from the end of month one until the end of month eight. The estimated mean trajectories of the classroom performance under the four embedded DTRs are shown in Figure 5.

The DTR (BMOD, BMOD+MED) is estimated to have the smallest AUC among the four embedded DTRs, and it differs significantly from the two DTRs that start with MED.
FIG. 5. Estimated mean trajectories under the embedded DTRs of the ADHD SMART.

The two MED DTRs are identical in terms of AUC. However, the two DTRs starting with BMOD seem to differ. Specifically, as suggested by the estimated coefficients, the slope of DTR (BMOD, BMOD+MED) after $t = 2$ is significantly positive (0.09; 95%CI (0.03, 0.15)); on the other hand, (BMOD, INT) has a quadratic trajectory with the second-order coefficient significantly negative (-0.04; 95%CI (-0.08, 0)), and the two MED DTRs both have a slope not significantly different from zero after $t = 3$. The data suggest that (BMOD, BMOD+MED) is the only embedded DTR that maintains a trend of improvement after $t = 2$. In summary, assigning MED initially seems to yield a more positive outcome than assigning BMOD initially in the short term, but the performance of children who initially receive BMOD improves within a wider range of time. In addition, there is no evidence that the two DTRs starting with MED differ in terms of their second-stage trajectories, but the
two DTRs beginning with BMOD differ markedly in terms of their second-stage trajectories.

C. Analysis of the ExTENd SMART Data

Our analysis of the ExTENd SMART data \((N = 250)\) is based on the flexible regression splines model discussed in Section III.D (details are presented in Appendix C). The repeated-measures outcome is the Penn Alcohol Craving Scale (PACS; Flannery et al. (1999)); values of this variable are reverse coded (ranging from 0 to 30), such that higher values indicate less alcohol craving, which is more favorable. Recall that in this study there were two definitions of non-response: stringent and lenient definitions. The weight at the first stage is estimated using age, gender, pre-study percent days heavy drinking, PACS at the screening visit and the first stage one visit; the weight at the second stage is estimated using age, PACS at the first and the last stage one visits, the assigned non-response definition, indicator of response to the first stage treatment, duration of stage one.

The estimated mean trajectories for PACS under the eight embedded DTRs are shown in Figure 6. The estimated AUCs for the eight embedded DTRs are reported in Table V. AUC/16 can now be interpreted as the average alcohol craving from entry to study to the end of week 16. The estimated trajectories imply that outcomes improve over time, on average over all eight embedded DTRs. DTRs that utilize the lenient definition for non-response were estimated to have better PACS outcomes (less alcohol craving) than DTRs that use the stringent definition. In particular, the DTR with the highest AUC (21.19; 95%CI (20.1, 22.3)) utilizes the lenient definition and assigns UC to responders and Placebo+CBI to non-responders. There were no significant differences between the eight DTRs in terms of the AUCs.

VI. SIMULATIONS

A small set of simulation experiments were conducted to investigate the importance of incorporating the unique features of a SMART in repeated-measures models comparing em-
FIG. 6. Estimated mean trajectories under the embedded DTRs of the ExTENd SMART. a1 (the definition for non-response) and a2 (stage two treatment regime) jointly specify the eight embedded DTRs.

bedded DTRs. In particular, we compared the bias and relative efficiency of estimators from a repeated-measures model that incorporates the features of a SMART versus traditional repeated-measures models that ignore these features. Data \((X, Y_0, A_1, Y_{12}, R, A_2, Y_{24}, Y_{36})\) were generated to mimic the autism SMART study. \(X\) is a 4-dimensional pre-treatment covariate for age, gender, indicator of African American, indicator of Caucasian; \(A_1\) is an indicator for the first-stage treatment (\(A_1 = 1\) for BLI, \(A_1 = -1\) for BLI+AAC); \(R\) is an indicator of early response (\(R = 1\)) versus slow response (\(R = 0\)); observations with \(A_1 = 1\) and \(R = 0\) have an indicator \(A_2\) for second-stage treatment (\(A_2 = 1\) for intensified BLI, or \(A_2 = -1\) for BLI+AAC); \(Y_t\) denotes the repeated-measures outcome at week \(t\).
It is well known that bias in the estimated comparisons between the DTRs is expected to occur under misspecified models (Orellana et al., 2010). Here we focus on a type of model misspecification that is specific to the analysis of repeated-measures data in a SMART. We adopt a series of data-generative models under which the mean trajectory of DTR (-1, ·) is maintained to be linear, and the average of the two mean trajectories of DTRs (1, 1) and (1, -1) is maintained to be linear. Recall that DTRs (1, 1) and (1, -1) ought to share trajectories up to $t = 12$. We create a series of models by varying the extent to which the trajectories of (1, 1) and (1, -1) deviate from the average between them, thus deviating from being linear. More specifically, we let the mean trajectories of (1, 1) and (1, -1) be two piecewise linear curves that share the path from $t = 0$ to $t = 12$. To quantify the magnitude of the deviation from linear, we conceptualize an effect size in terms of the comparison of AUCs between DTRs (1, 1) and (1, -1); this is operationalized as the true difference between the two AUCs divided by the pooled standard deviation in person-specific AUCs in each DTR group. Data sets with effect sizes equal to 0, 0.2, 0.5 and 0.8 and with sample size $N = 100$ and $N = 300$ are generated (details provided in Appendix A). Note that a zero effect size corresponds to the case where the two DTRs (1, 1) and (1, -1) do not differ over the entire course of the study; thus in this case both DTRs have a linear mean trajectory.

For each data-generative scenario, we fit three models: (a) the model shown in Equation (1); (b) a linear slopes model, in which the marginal trajectory of each embedded DTR is assumed to be linear; (c) a quadratic model, in which the marginal trajectory of each embedded DTR is assumed to be quadratic. Models (b) and (c) do not impose the constraint that DTRs (1, 1) and (1, -1) share the same trajectory until the end of the first treatment stage; in other words, the treatment stage transition is not explicitly accounted for in those two models. In all cases, the estimator for the repeated-measures models utilizes an independence working correlation.

We present results for two pairwise comparisons: $\Delta_{1}^{AUC}$ (the difference in AUC between DTRs (1, 1) and (1, -1)) and $\Delta_{2}^{AUC}$ (the difference in AUC between DTRs (-1, ·) and (1, -1)). We report the bias in the estimates when using the slopes model (SL) and quadratic
model (QD), and the ratio of MSE of estimators arising from SL and QD models over the MSE of estimators arising from the model (a). As SL and QD are correctly specified models only in the scenario with zero effect size, we expect to see bias in all scenarios except zero effect size. On the other hand, model (a) is a correctly specified model across all simulation scenarios. However, since SL model is more parsimonious than model (a), for small effect sizes we expect SL model to have smaller MSE than model (a).

Results are shown in Table VI. We notice that, as expected, SL and QD models produce biased estimates when they are not correctly specified (i.e., effect size not equal to zero). However, SL model has a smaller MSE than model (a) in some non-zero effect size cases; in particular, when the sample size is small ($N = 100$), SL model has a smaller MSE than model (a) for the estimation of $\Delta_2^{AUC}$ unless the effect size is big (this is when there is severe mis-specification when assuming the slopes model). This is due to the bias-variance tradeoff; SL model is more parsimonious thus may have smaller MSE when the induced bias is larger. This tradeoff can also be appreciated by noticing that, as the sample size increases, model (a) starts to outperform SL model under conditions with small effect sizes. Interestingly, for the estimation of $\Delta_1^{AUC}$, model (1) is better than SL model uniformly under all simulation scenarios. This can be intuitively explained by the fact that, the information that DTRs (1, 1) and (1, -1) share trajectory from $t = 0$ to $t = 12$ is particularly useful for the estimation of the AUC contrast between these two DTRs; this information is imposed in model (a) but not in SL model thus has to be estimated from SL model. We also notice that QD model always leads to a larger MSE than model (a), for estimation of both contrasts and across sample sizes.

These results suggest that it is important to account for the unique features of a SMART in the analysis of repeated-measures data. More traditional models such as the slopes model or the quadratic model (these are the types of models often used in the analysis of three-arm RCTs) do not effectively utilize known information about the SMART study design and may result in bias and efficiency loss, particularly when the sample size is moderate. The efficiency loss for certain estimands appears to occur even in settings where the true mean
trajectories do not deviate much from a slopes model or a quadratic model.

In online appendix, we provide additional simulation and results that examine (1) the extent to which efficiency is improved when adopting a non-independent working correlation structure in the estimation, for varying levels of true within-person correlations among \( Y_t \); and (2) the performance of confidence intervals constructed based on the asymptotic standard error.

VII. DISCUSSION

This manuscript provides modeling guidelines for comparing DTRs based on repeated-measures outcomes arising from a SMART. Three distinct SMART study designs were considered. The autism SMART has a relatively simple design, with only three embedded DTRs, and all patients transitioned to the second stage at the same time. In addition, there are only four measurement occasions during the entire study. Therefore, we suggested the piecewise linear model. In the ADHD SMART, non-responders transitioned to the second stage at different time points, and the transition times vary between two initial treatment groups. Thus we recommended a parametric model that accommodates these features. The ExTENd SMART differs from the other two SMARTs in that both responders and non-responders were re-randomized, but with different transition times to second stage. There are more DTRs embedded in this study (i.e., eight DTRs) and more measurement occasions. Thus we decided to model the trajectories of all embedded DTRs using regression splines that are properly constrained to respect the relationship among the embedded DTRs. In practice, decisions about how to appropriately model repeated measures arising from SMARTs should be contingent on when patients transition between treatment stages, positions of outcome measurement occasions relative to treatment stages, and subject-specific knowledge about the developmental pattern of the repeated-measures outcome.

In additional simulations not reported here we discovered that including repeated-measures outcomes before re-randomization in the model for estimating the true known
weight seems to play a similar role as specifying a non-independent working correlation structure in the GEE implementation, for the purpose of improving the efficiency of the estimator. However, this was in simulations mimicking the autism SMART with just two measurement occasions in the second stage. One advantage of the approach of using non-independent working correlation is that we are then able to utilize correlation among repeated-measures outcomes that all belong to the second treatment stage, because those outcomes cannot be included in the model for estimating weights. This might be particularly helpful in SMART studies where fewer repeated-measures outcomes are collected during the first treatment stage than during the subsequent treatment stages.

There has been debate in the field about whether the repeated measure at baseline should be considered a covariate or a dependent variable (Liu et al., 2009). In this technical report we chose to treat baseline as part of the repeated-measures outcome, when the measurement is available at baseline (in the ADHD SMART, it was not). We think this approach provides researchers with a more complete picture of the developmental trajectory associated with each DTR, because we are able to capture the change in the repeated measures from entry to the study.

The ExTENd SMART contains more subtle features that may have implications on modeling repeated measures; we did not investigate these in this report. For example, the initial randomization is between two distinct criteria for non-response, instead of between two distinct treatments or interventions, as in most other trials. This implies that two DTRs that differ in the criterion for non-response can only start to differ, after the participant meets the more stringent non-response criterion. In other words, there is a chance for all the embedded DTRs to share one mean trajectory during the first few weeks of the study. In addition, non-responders were blinded to the re-randomization, but responders were not (due to the nature of the treatments); this might have implications for modeling repeated-measures data in ExTENd. In future work we will extend the guidelines provided here to accommodate other unique features of SMART designs like ExTENd.

This work can also be extended readily in a number of directions. One natural extension
is to consider different link functions in the GEE model to examine how DTRs differ based on trajectories of categorical, count or ordinal outcomes. A second extension is to the analysis of cluster- (or group-) randomized SMARTs in which clusters are randomized sequentially, yet the primary outcome is measured at the level of individuals nested within clusters (Kilbourne et al., 2013); this is a setting where GEE methods are often used to account for clustering of individuals (patients) within clusters (sites).

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APPENDIX A: DETAILS CONCERNING THE DATA-GENERATIVE MODELS FOR THE SIMULATION

In the simulation in Section VI, we illustrate the importance of considering the special features of SMART designs in the modeling of repeated measures from SMART trials, by comparing a repeated-measures model that incorporates SMART features with more traditional longitudinal models like slopes and quadratic models. Here we provide additional details about the data-generative models used in this simulation. We adopted a series of data-generative models under which the mean trajectories of DTR (-1, ·) is maintained to be linear, and the average of the two mean trajectories of DTRs (1, 1) and (1, -1) is maintained to be linear; each data-generative model in the series is indexed by a parameter \( \theta > 0 \), which quantifies the extent to which the trajectories of DTRs (1, 1) and (1, -1) deflect at \( t = 12 \).

We generate data \((X, Y_0, A_1, Y_{12}, R, A_2, Y_{24}, Y_{36})\) for each individual in a sample of size
\( N. \)

- \( X \) includes six mean-centered baseline covariates: age, gender, indicator of African American, indicator of Caucasian, indicator of Hispanic, indicator of Asian. (Note that in the simulation experiments, the marginal model we fit for repeated measures only includes the first four covariates in \( X \) to avoid rank deficient problem in the estimation) \( X \) is sampled (with replacement) from the real autism SMART data. For notational simplicity, we let \( X \) below always contain intercept as the first coordinate.

- Generate \( Y_0 = \eta_0^T X + \epsilon_0 \), where \( \epsilon_0 \sim N(0, \sigma^2) \).

- Generate \( A_1 \) to be -1 or 1 with equal probability.

- Generate \( Y_{12} = \eta_{11}^T X + \eta_{12} Y_0 + \beta_{11} A_1 + \epsilon_1 \), where \( \epsilon_1 \sim N(0, \sigma^2) \).

- Generate \( A_2 \) to be -1 or 1 with equal probability, among individuals with \( A_1 = 1 \) and \( R = 0 \); otherwise \( A_2 = 0 \).

- Generate \( Y_{24} = \eta_{21}^T X + \eta_{22} Y_0 + \eta_{23} A_1 + \eta_{24} Y_1 + \beta_{21} (1 - R) (A_1 + 1) A_2 + \epsilon_2 \), where \( \beta_{21} = -\theta \) and \( \epsilon_2 \sim N(0, \sigma^2) \).

- Generate \( Y_{36} = \eta_{31}^T X + \eta_{32} Y_0 + \eta_{33} A_1 + \eta_{34} Y_1 + \beta_{31} (1 - R) (A_1 + 1) A_2 + \epsilon_3 \), where \( \eta_{31} = 2\eta_{21}, \eta_{32} = 2\eta_{22}, \eta_{33} = 2\eta_{23}, \eta_{34} = 2\eta_{24} - 1 \), \( \beta_{31} = 2\beta_{21} = -2\theta \) and \( \epsilon_3 \sim N(0, \sigma^2) \).

- The values of the coefficients mentioned above:

\[
\begin{align*}
\eta_0 &= (29.5, -5.1, -16.3, 0, 14.3, -11.8, 0.5), \\
\sigma &= 10, \\
\eta_{11} &= (23.46, 1.4, -3.0, 16.6, 11.1, 6.5, 22.5), \\
\eta_{12} &= 0.3, \\
\beta_{11} &= -1, \\
\eta_{21} &= (22.758, 1.20, 4.33, 12.33, 4.00, 7.53, 7.47), \\
\eta_{22} &= 0.2, \\
\eta_{23} &= -1.8, \\
\eta_{24} &= 0.2, \end{align*}
\]

In order to have data-generative models that are reasonable, we conceptualize an effect size in terms of the contrast in AUC between two embedded DTRs. We define the effect size of the comparison between DTR (1, 1) and DTR (1, -1) as the ratio of the difference in their AUCs over the pooled standard deviation of “a person-specific AUC” between the
two DTR groups. More specifically, we operationalize the person-specific AUC as $12(Y_6/2 + Y_{12} + Y_{24} + Y_{36}/2)$ for each individual. Let $\sigma_{(1,1)}$ denote the standard deviation of this person-specific AUC under DTR $(1, 1)$ and $\sigma_{(1,-1)}$ denote the standard deviation of this person-specific AUC under DTR $(1, -1)$. Then the effect size mentioned above can be written as $(AUC_{(1,1)} - AUC_{(1,-1)})/\left(\sigma^2_{(1,1)} + \sigma^2_{(1,-1)}\right)/2$. This measure quantifies the extent to which DTRs $(1, 1)$ and $(1, -1)$ differ throughout the entire study period.

Figure 7 shows the true mean trajectories of the repeated measures under the three embedded DTRs, in each of the four data-generative models (with effect size defined earlier equal to 0, 0.2, 0.5, 0.8) that we use in our simulation experiments. In all of four data-generative models, the effect size in terms of the comparison between DTR $(-1, \cdot)$ and the average of DTRs $(1, 1)$ and $(1, -1)$ is kept at around 0.4.

**APPENDIX B: DETAILS CONCERNING THE ANALYSIS OF REPEATED-MEASURES DATA IN THE ADHD STUDY**

For individual $i$, we observe $X_i, A_{1,i}, R_i, M_i, A_{2,i}$ and repeated measures $Y_{1,i}, \ldots, Y_{8,i}$. $A_1 = 1$ denotes that the individual received low-intensity BMOD and $A_1 = -1$ denotes that the individual received low-dose medication. $R$ indicates whether the individual was responding until the end of the study. When $R = 0$ (i.e., the individual became a non-responder during the study), $M$ denotes the time (in months) of non-response and $A_2$ denotes whether ($A_2 = 1$) the initial treatment was intensified or ($A_2 = -1$) the initial treatment was augmented with the alternative treatment.

The repeated-measures model proposed in (2) was estimated using the estimator presented in (3). In particular, the treatment sequence of each individual is consistent with either one or two of the embedded DTRs. An individual’s treatment sequence is consistent with only one embedded DTR if this individual was a non-responder (e.g., a non-responder to BMOD re-randomized to INT is only consistent with DTR (BMOD, INT)). An individual’s treatment sequence is consistent with two embedded DTRs if this individual was a
FIG. 7. True mean trajectories of the repeated measures under the embedded DTRs, under four data-generative models corresponding to effect size (of the contrast in AUC between DTR (1, 1) and (1, -1)) = 0, 0.2, 0.5, 0.8.

The weight $W$ in (3) is the inverse probability of an individual receiving the treatment sequence that was assigned. Therefore, responders receive a weight equal to 2 (they were randomized only once to two options) and non-responders receive a weight equal
to 4 (they were randomized twice, each time to two options). In our data analysis, however, we estimate these known weights using covariates specified in Section V.B to improve the statistical efficiency.

**APPENDIX C: DETAILS CONCERNING THE ANALYSIS OF REPEATED-MEASURES DATA IN THE EXTEND STUDY**

Given the many measurement occasions of the repeated-measures outcome, we adopted a piecewise splines model. Here we describe the details. From \( t = 0 \) to \( t = 2 \), we let the mean trajectory under DTR \((a_1, a_{2R}, a_{2NR})\) be a regression spline that is only determined by \( a_1 \) while sharing the same intercept. From \( t = 2 \) to \( t = 8 \), we let the mean trajectory under the DTR \((a_1, a_{2R}, a_{2NR})\) be a regression spline that continuously connects to the trajectory before \( t = 2 \), and is only determined by \((a_1, a_{2NR})\). From \( t = 8 \) to \( t = 16 \), we let the marginal mean under the DTR \((a_1, a_{2R}, a_{2NR})\) be a regression spline that continuously connects to the trajectory before \( t = 8 \), and can vary with \((a_1, a_{2R}, a_{2NR})\). For model simplicity, all the b-spline bases are of degree 2. We apply internal knots at \( t = 5 \) (midway from \( t = 2 \) to \( t = 8 \)) and \( t = 12 \) (midway from \( t = 8 \) to \( t = 16 \)).

A regression splines model can be viewed as a linear model, with properly chosen functions of b-spline bases as predictors. Therefore, the estimator presented in (3) can be readily applied. More specifically, in the ExTENd study, each individual’s treatment sequence is consistent with two embedded DTRs. For example, a patient who was assigned the lenient early non-response definition and later transitioned to stage two as a responder and received TDM was consistent with the following two DTRs: \((a_1, a_{2R}, a_{2NR})=(\text{lenient}, \text{TDM}, \text{NTX+CBI})\) and \((a_1, a_{2R}, a_{2NR})=(\text{lenient}, \text{TDM}, \text{Placebo+CBI})\). The weight in (3) is equal to 4 for any individual, because in the ExTENd study each individual was randomized twice, each time to one of two options. In our data analysis, we estimate these known weights using covariates specified in Section V.C to improve the statistical efficiency.
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### TABLE I. Embedded DTRs in tge autism SMART (with the labels).

<table>
<thead>
<tr>
<th>Label</th>
<th>Treatment decision rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTR #1 (1, -1)</td>
<td>Begin treatment with BLI for 12 weeks. At the end of week 12, if the child does not show early sign of response, augment BLI with AAC for 12 weeks. Otherwise, continue with BLI for another 12 weeks.</td>
</tr>
<tr>
<td>DTR #2 (1, 1)</td>
<td>Begin treatment with BLI for 12 weeks. At the end of week 12, if the child does not show early sign of response, intensify BLI for 12 weeks. Otherwise, continue with BLI for another 12 weeks.</td>
</tr>
<tr>
<td>DTR #3 (-1, .)</td>
<td>Begin treatment with BLI+AAC for 12 weeks. At the end of week 12, if the child does not show early sign of response, intensify BLI+AAC for 12 weeks. Otherwise, continue with BLI+AAC for another 12 weeks.</td>
</tr>
</tbody>
</table>
TABLE II. Design features of ExTENd study and their implications on modeling.

<table>
<thead>
<tr>
<th>Design features</th>
<th>Implications for repeated-measures modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization is (or should be) stratified on baseline measurements; there is no difference in anticipatory effect among the eight DTRs.</td>
<td>Trajectories of all the eight DTRs have the same intercept.</td>
</tr>
<tr>
<td>Patients became responders only if they stayed in stage one for eight weeks without hitting the assigned trigger. Once they became responders at the last visit of stage one, the initial visit of stage two was scheduled to be immediately after that, at which week eight PACS was measured. Re-randomization for responders is (or should be) stratified on measurements up to the initial visit of stage two.</td>
<td>A pair of DTRs that only differ in $a_{2R}$ (the second-stage treatment for responders) should share the same trajectory until the end of week eight, and may differ from then on.</td>
</tr>
<tr>
<td>Patients transitioned to stage two at as early as week two as early non-responders, then they had the initial visit of stage two immediately after the end visit of stage one. Re-randomization for non-responders is (or should be) stratified on measurements up to the initial visit of stage two. In particular, re-randomization for non-responders is (or should be) stratified on measurements up to week two.</td>
<td>A pair of DTRs that only differ in $a_{2NR}$ (the second-stage treatment for non-responders) should share the same trajectory until the end of week two, and may differ from then on.</td>
</tr>
</tbody>
</table>
TABLE III. An analysis of the repeated-measures outcomes from the autism SMART. The reported summary of each DTR and the comparison between DTRs concerns AUC/36.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$ (Intercept)</td>
<td>29.57</td>
<td>4.53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\eta_1$ (age)</td>
<td>-3.63</td>
<td>3.59</td>
<td>0.32</td>
</tr>
<tr>
<td>$\eta_2$ (male)</td>
<td>-9.39</td>
<td>15.73</td>
<td>0.55</td>
</tr>
<tr>
<td>$\eta_3$ (AfricanAmerican)</td>
<td>1.04</td>
<td>13.92</td>
<td>0.94</td>
</tr>
<tr>
<td>$\eta_4$ (Caucasian)</td>
<td>1.09</td>
<td>8.18</td>
<td>0.89</td>
</tr>
<tr>
<td>$\beta_1$ (time; stage one)</td>
<td>1.39</td>
<td>0.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\beta_2$ (time×$A_1$; stage one)</td>
<td>-0.80</td>
<td>0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>$\beta_3$ (time; stage two)</td>
<td>0.12</td>
<td>0.20</td>
<td>0.54</td>
</tr>
<tr>
<td>$\beta_4$ (time×$A_1$; stage two)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.33</td>
</tr>
<tr>
<td>$\beta_5$ (time×$A_1A_2$; stage two)</td>
<td>-0.08</td>
<td>0.14</td>
<td>0.57</td>
</tr>
<tr>
<td>(BLI,INT)</td>
<td>37.38</td>
<td>4.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(BLI,BLI+AAC)</td>
<td>38.68</td>
<td>4.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(BLI+AAC,·)</td>
<td>50.84</td>
<td>4.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(BLI,INT) vs (BLI,BLI+AAC)</td>
<td>-1.30</td>
<td>2.24</td>
<td>0.57</td>
</tr>
<tr>
<td>(BLI+AAC,·) vs (BLI,BLI+AAC)</td>
<td>12.16</td>
<td>5.44</td>
<td>0.03</td>
</tr>
<tr>
<td>(BLI+AAC,·) vs (BLI,INT)</td>
<td>13.46</td>
<td>5.58</td>
<td>0.02</td>
</tr>
</tbody>
</table>
TABLE IV. An analysis of the repeated-measures outcomes from the ADHD SMART. The reported summary of each DTR and the comparison between DTRs concerns AUC/7.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_0 ) (Average Intercept of BMOD and MED)</td>
<td>2.31</td>
<td>0.12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>( \beta_1 ) (A1; baseline)</td>
<td>-0.25</td>
<td>0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>( \beta_2 ) (time; t \leq 2 under BMOD)</td>
<td>-0.01</td>
<td>0.16</td>
<td>0.93</td>
</tr>
<tr>
<td>( \beta_3 ) (time; t &gt; 2 under (BMOD,INT))</td>
<td>0.34</td>
<td>0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>( \beta_4 ) (time^2; t &gt; 2 under (BMOD,INT))</td>
<td>-0.04</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>( \beta_5 ) (time; t &gt; 2 under (BMOD,BMOD+MED))</td>
<td>0.09</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>( \beta_6 ) (time; t \leq 3 under MED)</td>
<td>0.11</td>
<td>0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>( \beta_7 ) (time; t &gt; 3 under (MED,INT))</td>
<td>-0.03</td>
<td>0.04</td>
<td>0.41</td>
</tr>
<tr>
<td>( \beta_8 ) (time; t &gt; 3 under (MED,MED+BMOD))</td>
<td>-0.05</td>
<td>0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>(BMOD,BMOD+MED)</td>
<td>2.29</td>
<td>0.14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(BMOD,INT)</td>
<td>2.48</td>
<td>0.13</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(MED,MED+BMOD)</td>
<td>2.67</td>
<td>0.13</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(MED,INT)</td>
<td>2.69</td>
<td>0.12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(BMOD,BMOD+MED) vs (BMOD,INT)</td>
<td>-0.19</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>(BMOD,BMOD+MED) vs (MED,MED+BMOD)</td>
<td>-0.38</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>(BMOD,BMOD+MED) vs (MED,INT)</td>
<td>-0.41</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td>(BMOD,INT) vs (MED,MED+BMOD)</td>
<td>-0.19</td>
<td>0.18</td>
<td>0.30</td>
</tr>
<tr>
<td>(BMOD,INT) vs (MED,INT)</td>
<td>-0.21</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>(MED,MED+BMOD) vs (MED,INT)</td>
<td>-0.03</td>
<td>0.07</td>
<td>0.71</td>
</tr>
</tbody>
</table>
TABLE V. An analysis of the repeated-measures outcomes from the ExTENd SMART.

<table>
<thead>
<tr>
<th>Embedded DTR</th>
<th>Estimate AUC/16</th>
<th>SE of AUC/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>(LNT,TDM,NTX)</td>
<td>20.65</td>
<td>0.56</td>
</tr>
<tr>
<td>(LNT,TDM,PLC)</td>
<td>21.02</td>
<td>0.55</td>
</tr>
<tr>
<td>(LNT,UC,NTX)</td>
<td>20.83</td>
<td>0.57</td>
</tr>
<tr>
<td>(LNT,UC,PLC)</td>
<td>21.19</td>
<td>0.55</td>
</tr>
<tr>
<td>(STRGT,TDM,NTX)</td>
<td>20.18</td>
<td>0.59</td>
</tr>
<tr>
<td>(STRGT,TDM,PLC)</td>
<td>20.18</td>
<td>0.56</td>
</tr>
<tr>
<td>(STRGT,UC,NTX)</td>
<td>20.04</td>
<td>0.57</td>
</tr>
<tr>
<td>(STRGT,UC,PLC)</td>
<td>20.03</td>
<td>0.58</td>
</tr>
</tbody>
</table>
TABLE VI. Bias and Relative MSE (in relation to the proposed repeated-measures model that respects the design features of SMART) of estimates from slope model and quadratic model. $\Delta_1^{AUC} = $ the constrast in AUC between DTRs (1, 1) and (1, -1); $\Delta_2^{AUC} = $ the contrast in AUC between DTRs (-1, ·) and (1, -1). SL = slope model, QD = quadratic model. Bias that significantly differs from zero is in bold.

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>SL</th>
<th>QD</th>
<th>Bias x 100</th>
<th>RMSE</th>
<th>SL</th>
<th>QD</th>
<th>Bias x 100</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>1.7</td>
<td>1.67</td>
<td>1.87</td>
<td>-5.2</td>
<td>-1.9</td>
<td>0.71</td>
<td>1.55</td>
</tr>
<tr>
<td>0.2</td>
<td>-35.4</td>
<td>13.5</td>
<td>1.89</td>
<td>1.73</td>
<td>-19.7</td>
<td>-0.7</td>
<td>0.77</td>
<td>1.48</td>
</tr>
<tr>
<td>0.5</td>
<td>-98.6</td>
<td>33.6</td>
<td>2.7</td>
<td>1.6</td>
<td>-50.1</td>
<td>14.9</td>
<td>0.98</td>
<td>1.49</td>
</tr>
<tr>
<td>0.8</td>
<td>-161.8</td>
<td>65.6</td>
<td>2.91</td>
<td>1.35</td>
<td>-79</td>
<td>33.9</td>
<td>1.32</td>
<td>1.37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>SL</th>
<th>QD</th>
<th>Bias x 100</th>
<th>RMSE</th>
<th>SL</th>
<th>QD</th>
<th>Bias x 100</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>0</td>
<td>1.71</td>
<td>1.71</td>
<td>3.4</td>
<td>5.4</td>
<td>0.72</td>
<td>1.43</td>
</tr>
<tr>
<td>0.2</td>
<td>-41</td>
<td>10.7</td>
<td>2.57</td>
<td>1.69</td>
<td>-20.9</td>
<td>6.2</td>
<td>0.85</td>
<td>1.45</td>
</tr>
<tr>
<td>0.5</td>
<td>-105.5</td>
<td>25.7</td>
<td>5.17</td>
<td>1.57</td>
<td>-54.5</td>
<td>10.7</td>
<td>1.53</td>
<td>1.44</td>
</tr>
<tr>
<td>0.8</td>
<td>-189.2</td>
<td>36</td>
<td>7.87</td>
<td>1.34</td>
<td>-96</td>
<td>17</td>
<td>2.97</td>
<td>1.38</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

FIG. 1 An example SMART for the development of a DTR for children with autism who are minimally verbal. R = randomization. BLI = behavioral language intervention. AAC = augmentative or alternative communication approach. 6

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