Sequential Multiple Assignment Randomization Trials with Enrichment Design

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SUMMARY: Sequential multiple assignment randomization trial (SMART) is a powerful design to study Dynamic Treatment Regimes (DTRs) and allows causal comparisons of DTRs.To handle practical challenges of SMART study, we propose a SMART with Enrichment (SMARTER) design, which can potentially improve the design efficiency, shorten the recruitment period, and reduce the trial duration to make SMART more practical with limited time and resource. Specifically, at each subsequent stage of a SMART, we enrich the study sample with new patients who have received previous stages' treatments in a naturalistic fashion without randomization, and only randomize them among the current stage treatment options. One extreme case of the SMARTER is to synthesize separate independent single-stage randomized trials with patients who have received previous stage treatments. We show data from SMARTER allows for unbiased estimation of DTRs as SMART does under certain assumptions. Furthermore, we show analytically that the efficiency gain of the new design over SMART can be significant especially when the dropout rate is high. Lastly, extensive simulation studies are performed to demonstrate performance of SMARTER design, and sample size estimation in a scenario informed by real data from a SMART study is presented.

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1. Introduction

Dynamic Treatment Regimes (DTRs), also referred to as adaptive treatment regimes or tailored treatment regimens, are sequential treatment rules tailored at each stage by patients' time-varying characteristics and intermediate treatment responses (Lavori et al., 2000; Murphy et al., 2007; Dawson and Lavori, 2004). For example, an oncologist aiming to prolong survival for a cancer patient might use intermediate outcomes such as patient's tumor response to induction therapy to guide the use of second-line therapy. Sequential multiple assignment randomization trials (SMARTs) (Lavori and Dawson, 2000, 2004; Murphy, 2005) generalize conventional randomized clinical trials to make causal comparisons of such DTRs. In SMARTs, patients are randomized to different treatments at each critical decision stage, where randomization probabilities may depend on patients' time-varying information up to that stage. These trials also provide rich information to infer optimal treatment regimes tailored to individual patients. Murphy (Murphy, 2005) provides inferences and sample size formula to compare two DTRs in SMARTs, Almirall et al. (Almirall et al., 2012) proposed to use SMART design as a pilot study for building effective DTRs, and Nahum-Shani et al. (Nahum-Shani et al., 2012) illustrated several important design issues and primary analyses for SMART studies.

We use a real study (Kasari et al., 2014) to illustrate DTR and concepts in SMART. Kasari et al. (2014) conducted a SMART on communication intervention for minimal verbally children with autism. The study is a two-stage SMART targeted on testing the effect of a speech-generating device (SGD). In the first stage, 61 children were randomized to a blended developmental/behavioral intervention (JASP+EMT) with or without augmentation of a SGD for 12 weeks with equal probability. At the end of the 12th week, children were assessed for early response versus slow response to stage 1 treatment. In the second stage, the early-responders continued with the first stage treatments. The slow-responders to (JASP+EMT)

were randomized to (JASP+EMT+SGD) or intensified (JASP+EMT+SGD) with equal probability. The second stage lasted 12 weeks and followed by a follow up stage of 12 weeks. In this study, the primary aim was to compare the first stage treatment options SGD (JASP+EMT+SGD) verses spoken words alone (JASP+EMT). Secondary aim was to compare the dynamic treatment regimes (DTRs), namely: 1. beginning with JASP+EMT+SGD and intensifying JASP+EMT+SGD for slow responders; 2 beginning with JASP+EMT and to increase the intensity for slow responders; 3. beginning with JASP+EMT and to switch JASP+EMT+SGD for slow responders.

Study dropout is a common phenomenon in randomized clinical trials (RCTs) regardless of investigator's best efforts to keep patients in the study. For example, meta analyses of study dropout rate for RCTs of antipsychotic drugs reported an average attrition rate of greater than 30% (Martin et al., 2006; Kemmler et al., 2005). For multi-stage SMARTs, even higher dropout rate might be expected. Although smaller SMARTs maybe have lower drop out rate (e.g., 15% in Kasari et al., 2014), attrition is still an issue not to be ignored in the planning stage. In the Clinical Antipsychotic Trials of Intervention and Effectiveness (CATIE) study (Schneider et al., 2003), the attrition was high with 705 of 1460 patients (48%) staying for the entire 18 months. In a two-stage randomized trial on induction chemotherapies followed by maintenance chemotherapy with or without radiotherapy to the chest (Joss et al., 1994), only 118 of 266 patients (44%) entered the second stage randomization. Designing a SMART may thus require a larger sample size in the initial stage to ensure sufficient power for comparing DTRs in a multi-stage trial. In addition, it is time-consuming and challenging to manage and monitor a sequential multi-stage trial with a large sample size and long follow-up time. The time and resource constraints may limit the ability of SMART studies to answer many important clinical questions regarding DTRs.

In this work, we propose an innovative design and a meta-analytic approach to enrich

SMART sample and to synthesize single-stage trials without sacrificing the central feature of SMART to make causal conclusions. We show that the proposed SMART with Enrichment design (SMARTer) and its appropriate analysis method significantly boost the efficiency of SMART, address the attrition issue from the design and analysis perspective, improve practicability of SMART, and avoid pitfalls of incorrect inference on long term DTR effect when combining single-stage randomized trials. Specifically, the proposed methodology can potentially (1) extract information from patients dropping out from the first stage; (2) recruit and randomize additional patients to the second-stage treatments without requiring randomization of the first-stage treatments, and thus achieve the same or superior efficiency as if there were no dropouts, which reduces the sample size of the initial stage and the overall sample size; and (3) synthesize single-stage trials to integrate information to make causal inference on DTRs as is possible in a multi-stage SMART, while substantially shortening the trial time frame.

It is of interest to note that the proposed SMARTer design differs from an intuitive approach that pieces together results from separate randomized trials conducted at separate stages, as criticized in previous literature (Murphy et al., 2007; Collins et al., 2014). For the latter, an investigator may determine the best first-line treatment based on a conventional randomized trial comparing several first-line treatments and then next, compare second-line treatments for a new group of subjects already treated by the "best" first-stage treatment. Essentially, this intuitive approach compares available intervention options at each stage separately to infer the best DTR. It has several disadvantages (Murphy et al., 2007): first, it does not capture the delayed effect when the long term effect begins to appear in latter stages; second, it fails to take into account the prescriptive effect of an early stage treatment which may not yield a larger intermediate outcome; third, single-stage trials tend to enroll more homogeneous patients to increase power for detection of treatment differences whereas

SMART would not. In terms of design, SMARTER does not recommend enriching the sample with only the subjects who have received the "best" first-line treatment inferred from a single-stage trial. Instead, we recruit enrichment samples from subjects who have received any of the first-line treatments so that the enrich population includes patients with all possible combinations of both lines of treatments to properly account for delayed effect and prescriptive effect. The main focus of SMARTER design is to improve efficiency through enrichment samples who only receive randomization in the latter stages. In terms of the analysis, instead of inferring the best treatment from each single stage separately, SMARTER can infer optimal DTRs with backward induction algorithms such as Q-learning (Murphy et al., 2007), which uses the randomized samples for each stage including the enrichment participants.

This paper is structured as follows. In Section 2, we introduce SMARTER design and justify the validity under a causal inference framework. In Section 3, we provide the estimation and inference for estimating the mean outcome of a DTR and comparison of two DTRs. In Section 4, we study the efficiency of SMARTER as compared to SMART and compare their sample sizes. Extensive simulation study results are shown in Section 5 to examine the performance of SMARTER, the accuracy of the derived sample size formula, and the robustness of this design. In section 6, we illustrate the sample size calculation under design parameters informed by a real world SMART study of autism disorder. Section 7 provides some preliminary work of finding the optimal DTR based on a SMARTER design and concludes with some discussions.

2. SMARTer Design

2.1 *Rationales of the* SMARTer *Design*

The essential idea of a SMARTer design is that at the kth stage ($k > 1$), enrich the original SMART with new patients randomized among the kth stage treatment options. As illustrated in the flowchart Figure 1, consider enrichment for a two-stage SMART with no intermediate outcomes. Generalizations to more than two stages and including intermediate outcomes are similar. Assume that n patients are randomized at the first stage in a SMART. Some patients complete the first stage treatment and undergo the second stage randomization (group 1), while some patients drop out before the second stage randomization (group 2). To mitigate the problem of attrition after the first stage treatment, while the original SMART is progressing, we concurrently recruit m new patients as the enrichment sample (group 3). One key eligibility criterion for the enrichment group is that they have received one of the first stage treatments. However, their first stage treatments can be assigned in a naturalist fashion without randomization prior to the enrollment. For the enrichment subjects in group 3, their second-stage treatments will be randomized as in the original SMART.

Taking the autism study (Kasari et al., 2014) as an example, the primary outcome for this study was the total number of spontaneous communicative utterances (TSCU). The response status to the first stage treatment was the intermediate outcome that the second stage treatment choice and randomization probability depended on. For example, for a DTR starting with JASP+EMT, whether a patient participates in the second randomization to add SGD or intensify depends on whether he/she is a slow responder or not. Group 1 patients would be those who were randomized in the first stage and stayed through the trial until the end of the second stage. Group 2 patients include the 6 patients who dropped out after randomization in the first stage, and the additional 3 patients who dropped out after finishing first stage and on whom the intermediate response variables were recorded. In the

next few sections, we will provide analysis of efficiency and sample size computation for the enrichment group 3 patients in the new SMARTER design to estimate the mean outcome of a given DTR and compare DTRs.

The final analysis sample of SMARTER consists of three groups of patients (also shown in Figure 1). Specifically, group 1 is the n_1 SMART subjects who stay through two stages of randomization and treatments; group 2 is the n_2 SMART subjects who drop out before the second randomization; and group 3 is the m enrichment subjects who only receive the second-stage randomization with known first-stage treatment history. Let Z_i denote the indicator of stage 2 completion status for subject i, S_i denote pre-treatment information at stage 1, A_{ki} denote treatment at stage k ($k = 1, 2$), and Y_i denote the observed reward outcome from the study. Then SMARTER data consist of the data from the original SMART subjects, $(S_i, A_{1i}, Z_i A_{2i}, Z_i Y_i, i = 1, ..., n)$, and the data from the m enrichment subjects, $(S_j, A_{1j}, A_{2j}, Y_j, j = 1, ..., m)$. In the subsequent presentation, we assume S_i to take a finite number of discrete values for convenience.

[Figure 1 about here.]

To understand why SMARTER enables valid evaluation of DTRs under certain assumptions, we first focus on a two-stage trial and assume that there is no intermediate information after stage 1. For any DTR (d_1, d_2), a sequence of decision rules with d_k representing a function mapping historical information to the domain of A_k for $k = 1, 2$, our goal is to estimate the value function of (d_1, d_2) defined as $E[Y(d_1, d_2)]$. Here $Y(a_1, a_2)$ is the potential outcome associated with the treatment assignment (a_1, a_2). We assume the following conditions hold: (C.1) $Y = \sum_{a_1, a_2} Y(a_1, a_2) I(A_1 = a_1, A_2 = a_2)$; (C.2) The dropout is independent of $\{Y(a_1, a_2)\}$ given (A_1, S); (C.3) The conditional distribution of Y given (A_1, S, A_2) in the enrichment group is the same as that in the original SMART population. (C.4) The first stage

domain of A_1 (treatment options) for the enrichment group is identical to the treatment A_1 in the SMART population.

Condition (C.1) is the standard stable unit treatment value assumption (SUTVA) in causal inference. Condition (C.2) is the standard non-informative dropout or missing at random (MAR) assumption also required in any analysis of an RCT. The key condition (C.3) requires that the conditional treatment effect given S is the same between the original SMART samples and the enrichment samples. This assumption is important since if it is not satisfied, the data from the enrichment group cannot be used to complement the original SMART. Condition (C.4) ensures the first stage treatments are comparable in the SMART and enrichment samples.

Under conditions (C.1)–(C.4), we show SMARTER can provide an unbiased estimation of the average causal outcome for the DTR (d_1, d_2), that is, $E[Y(d_1, d_2)]$. The essential idea is that sequential ignorability assumption required to draw causal inference is satisfied in the enrichment sample when used to predict mean outcomes and compare second stage treatment options. In other words, due to sequential ignorability, potential outcomes $\{Y(a_1, a_2)\}$ are conditionally independent of A_2 given (A_1, S) in the enrichment sample, even if their first stage treatments can be received in a naturalistic fashion without randomization. When comparing first stage treatment options, we only use the non-dropouts from the original SMART and predicted outcomes for n_2 dropouts whose first stage treatments are randomized. Specifically, let $p_k(a_k|s_k)$ denote the randomization probability of A_k given a patient's covariates collected up to stage k, i.e., s_k. Note that for simplicity, here we assume second stage randomization probabilities depend on baseline covariates and first stage treatments. In Section 2.3, we generalize to allow them to depend on intermediate outcomes. Our key result is to show

$$E[Y(d_1, d_2)] = \mu_1 = \mu_2,$$

$$\text{where } \mu_1 = E_1\left[\frac{I(A_1 = d_1(S), A_2 = d_2(A_1, S))}{p_1(A_1|S)p_2(A_2|S, A_1)}Y\right], \mu_2 = E_2\left[\frac{I(A_1 = d_1(S))}{p_1(A_1|S)}Y^*\right],$$

$E_g[\cdot]$ denotes the expectation for subjects in group g, and Y^* denotes the conditional mean of Y given $(A_1, S, A_2 = d_2(A_1, S))$ for subjects in group 1 and 3. The rationale is that if this equality holds, then the average causal outcome, $E[Y(d_1, d_2)]$, can be estimated unbiasedly using the data from SMARTer since Y^*, $E_1[\cdot]$, and $E_2[\cdot]$ can be estimated unbiasedly using their corresponding empirical averages. There are three observations of this result: (1) Since group 1 subjects' final outcomes Y are observed, we estimate their average causal mean using their observed outcomes; (2) Group 2 subjects drop out after first-stage and have missing Y, but their outcomes can be estimated as Y^* from subjects in group 1 and 3; (3) Group 3 subjects contribute to the estimation through estimating missing outcomes for subjects in group 2.

To see why the above equalities hold, first note that under condition (C.1), we obtain

$$\mu_1 = E_1\left[\frac{I(A_1 = d_1(S), A_2 = d_2(A_1, S))}{p_1(A_1|S)p_2(A_2|S, A_1)}Y(d_1, d_2)\right].$$

By randomization, A_2 is independent of potential outcome $Y(d_1, d_2)$ given (S, A_1). Thus, since $E_1[\cdot]$ is equivalent to $E[\cdot]$ under the non-informative dropout condition (C.2), the above expression becomes

$$\mu_1 = E\left[\frac{I(A_1 = d_1(S))}{p_1(A_1|S)}Y(d_1, d_2)\right].$$

Furthermore, by randomization of A_1 in the first stage for group 1 subjects, we obtain the above equation to also equal the average causal outcome, i.e.,

$$\mu_1 = E\left[E\left\{\frac{I(A_1 = d_1(S))}{p_1(d_1|S)}|S\right\}E\left\{Y(d_1, d_2)|S\right\}\right] = E[Y(d_1, d_2)].$$

Next, due to randomization of A_2 for subjects in group 1 and group 3, under condition (C.3), we obtain

$$Y^* = E[Y(A_1, d_2(A_1, S))|A_1, S, A_2 = d_2(A_1, S)] = E[Y(A_1, d_2(A_1, S_1))|A_1, S].$$

Consequently,

$$\mu_2 = E\left[\frac{I(A_1 = d_1(S))}{p_1(A_1|S)} E[Y(A_1, d_2(A_1, S))|A_1, S]\right] = E\left[\frac{I(A_1 = d_1(S))}{p_1(A_1|S)} E[Y(d_1, d_2)|A_1, S]\right].$$

Again, by the randomization of A_1 for subjects in group 2, we conclude $\mu_2 = E[Y(d_1, d_2)]$.

2.2 *Value Estimation and Inference in* SMARTER

Given a DTR (d_1, d_2), for a patient with $S = s$ and treatment assignment $a_1 = d_1(s)$ and $a_2 = d_2(s, a_1)$, an estimator of the expected outcome value associated with this DTR is

$$\begin{aligned}\widehat{\mu}(d_1, d_2) = &\left\{\sum_{i=1}^{n}\left(Z_i \frac{I(A_{1i} = d_1(S_i), A_{2i} = d_2(S_i, A_{1i}))}{p(A_{1i}|S_i)p(A_{2i}|S_i, A_{1i})} + (1 - Z_i)\frac{I(A_{1i} = d_1(S_i))}{p(A_{1i}|S_i)}\right)\right\}^{-1} \\ &\times \left\{\sum_{i=1}^{n}\left(Z_i \frac{I(A_{1i} = d_1(S_i), A_{2i} = d_2(S_i, A_{1i}))}{p(A_{1i}|S_i)p(A_{2i}|S_i, A_{1i})} Y_i\right.\right. \\ &\left.\left. + (1 - Z_i)\frac{I(A_{1i} = d_1(S_i))}{p(A_{1i}|S_i)}\widehat{Y}(A_{1i}, d_2(S_i, A_{1i}), S_i)\right)\right\}, \qquad (1)\end{aligned}$$

where $\widehat{Y}(a_1, a_2, s)$ is the predicted outcomes for group 2 subjects using group 1 and group 3 data:

$$\widehat{Y}(a_1, a_2, s) = \frac{\sum_{i=1}^{n} Z_i Y_i I(A_{1i} = a_1, A_{2i} = a_2, S_i = s) + \sum_{j=1}^{m} Y_j I(A_{1j} = a_1, A_{2j} = a_2, S_j = s)}{\sum_{i=1}^{n} Z_i I(A_{1i} = a_1, A_{2i} = a_2, S_i = s) + \sum_{j=1}^{m} I(A_{1j} = a_1, A_{2j} = a_2, S_j = s)}.$$

The essential idea is to compute the average outcome for subjects in SMART using observed outcomes for group 1 and imputed outcomes for group 2 (imputed using group 1 and 3 data). The enrichment sample improves estimation efficiency through nonparametric imputation (simple average) for subjects in group 2. Note that from (1), even without an enrichment sample (i.e., $m = 0$), we can still impute group 2 subjects' outcomes using group 1 subjects' to improve efficiency with no bias. Thus the estimator in (1) deals with missing data issue for SMART design as well. It is clear that the estimator in (1) adheres to the intention-to-treatment principal (Fisher et al., 1989) such that all subjects randomized are analyzed according to their original treatment assignments.

Next, we derive the asymptotic variance formula for estimator (1) under the conditions (C.1) through (C.4) assuming $m = O(n)$. Specifically, we wish to obtain the asymptotic

expansion of $\widehat{\mu}(d_1, d_2) - \mu(d_1, d_2)$. To this end, we let $p(s)$ be the probability of $S = s$ and $p(a_1|s)$ be the randomization probability of $A_1 = a_1$ given $S = s$ in the SMART population in the first stage and let $p(a_2|s, a_1)$ be the randomization probability of $A_2 = a_2$ given $S = s$ and $A_1 = a_1$ in the second stage. These two conditional probabilities are known by design. Furthermore, we let $q(s)$ and $q(a_1|s)$ be the probability of enrichment sample with $S = s$ and receiving first-stage treatment $A = a_1$ given $S = s$. Note that due to the observational nature of the enrichment group for the first-stage treatment, $q(s)$ may not equal $p(s)$ and $q(a_1|s)$ may not equal $p(a_1|s)$. We let $\pi_1(a_1, a_2, s) = p(a_2|s, a_1)p(a_1|s)p(s)$, $\pi_2(a_1, a_2, s) = p(a_1|s)p(s)I(d_2(s, a_1) = a_2)$, and $\pi_3(a_1, a_2, s) = p(a_2|s, a_1)q(a_1|s)q(s)$. Finally, denote $\alpha(a_1, s) = P(Z = 1|A_1 = a_1, S = s)$, $\beta = m/n$, and $r(a_1, s) = q(a_1|s)q(s)/[p(a_1|s)p(s)]$.

We show in Appendix B the asymptotic variance of $\widehat{\mu}(d_1, d_2)$ is V/n, where

$$
\begin{aligned}
V \equiv\ & Var_s\left(Z\frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)}\right. \\
& \times \left\{(Y - \mu(d_1, d_2)) + \frac{1 - \alpha(A_1, S)}{\alpha(A_1, S) + \beta r(A_1, S)}(Y - E[Y|A_1, A_2, S])\right\} \\
& \left. + (1 - Z)\frac{I(A_1 = d_1(S))}{p(A_1|S)}E[Y - \mu(d_1, d_2)|A_1, A_2 = d_2(S, A_2), S]\right) \\
& + \beta Var_e\left(\frac{(1 - \alpha(A_1, S))\,(Y - E[Y|A_1, A_2, S])}{\alpha(A_1, S) + \beta r(A_1, S)}\,\frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)}\right).
\end{aligned}
$$

The first term is the variability from subjects in group 1 and imputing outcomes for group 2, and the second term is the variability from enrichment subjects in group 3. The variance can be estimated by its empirical form.

Finally, to compare two DTRs, we can use the difference of SMARTER estimators for two DTRs (d_1, d_2) and (d_1', d_2'), i.e., $\widehat{\mu}(d_1, d_2) - \widehat{\mu}(d_1', d_2')$. Then its asymptotic variance is

$V(\bar{d}_2, \bar{d}'_2)/n$, where

$$
\begin{aligned}
& V(\bar{d}_2, \bar{d}'_2) \\
\equiv\ & Var_s \Bigg\{ Z \frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)} \\
& \times \left((Y - \mu(d_1, d_2)) + \frac{1 - \alpha(A_1, S)}{\alpha(A_1, S) + \beta r(A_1, S)} (Y - E[Y|A_1, A_2, S]) \right) \\
& - Z \frac{I(A_1 = d'_1(S), A_2 = d'_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)} \\
& \times \left((Y - \mu(d'_1, d'_2)) + \frac{1 - \alpha(A_1, S)}{\alpha(A_1, S) + \beta r(A_1, S)} (Y - E[Y|A_1, A_2, S]) \right) \\
& + (1 - Z) \frac{I(A_1 = d_1(S))}{p(A_1|S)} E[Y - \mu(d_1, d_2)|A_1, A_2 = d_2(S, A_2), S] \\
& - (1 - Z) \frac{I(A_1 = d'_1(S))}{p(A_1|S)} E[Y - \mu(d'_1, d'_2)|A_1, A_2 = d'_2(S, A_2), S] \Bigg\} \\
+ & \beta Var_e \left[\frac{(1 - \alpha(A_1, S))\,(Y - E[Y|A_1, A_2, S])}{\alpha(A_1, S) + \beta r(A_1, S)} \frac{I(A_1 = d_1, A_2 = d_2) - I(A_1 = d'_1, A_2 = d'_2)}{p(A_1|S)p(A_2|S, A_1)} \right].
\end{aligned}
$$

This variance can also be estimated by its empirical form.

2.3 *Incorporating intermediate outcomes*

The previous section assumes no intermediate outcome is available especially for subjects who drop out from the SMART. When intermediate outcomes on these subjects are available, consider the DTR (d_1, d_2), where the treatment rule d_2 may depend on the intermediate outcome. In this case, the observed data from a SMARTER consist of $(S_{1i}, A_{1i}, S_{2i}, Z_i A_{2i}, Z_i Y_i), i = 1, ..., n$, for i in the original SMART group, and the enrichment group observations $(S_{1j}, A_{1j}, S_{2j}, A_{2j}, Y_j)$, $j = 1, ..., m$. Here, we use S_1 to denote pre-treatment covariates at stage 1 and S_2 to denote intermediate outcomes and other covariates collected prior to stage 2. For simplicity of derivation, we assume S_{1i} and S_{2j} to be discrete. Similar to (1), a consistent estimator of the associated value using both the SMART and enrichment observations is

$$\begin{aligned}\widehat{\mu}(d_1,d_2) &= \left\{\sum_{i=1}^{n}\left(Z_i\frac{I(A_{1i}=d_1(S_{1i}),A_{2i}=d_2(S_{1i},A_{1i},S_{2i}))}{p(A_{1i}|S_{1i})p(A_{2i}|S_{1i},A_{1i},S_{2i})}+(1-Z_i)\frac{I(A_{1i}=d_1(S_{1i}))}{p(A_{1i}|S_{1i})}\right)\right\}^{-1}\\ &\times\left\{\sum_{i=1}^{n}\left(Z_i\frac{I(A_{1i}=d_1(S_{1i}),A_{2i}=d_2))}{p(A_{1i}|S_{1i})p(A_{2i}|S_{1i},A_{1i},S_{2i})}Y_i\right.\right.\\ &\left.\left.+(1-Z_i)\frac{I(A_{1i}=d_1(S_{1i}))}{p(A_{1i}|S_{1i})}\widehat{Y}(A_{1i},d_2(S_{1i},A_{1i},S_{2i}),S_{1i},S_{2i})\right)\right\},\end{aligned}$$

where $\widehat{Y}(a_1,a_2,s)$ is the imputed outcome from the second-stage data given as

$$\frac{\sum_{i=1}^{n}Z_iY_iI(A_{1i}=a_1,A_{2i}=a_2,S_{1i}=s_1,S_{2i}=s_2)+\sum_{j=1}^{m}Y_jI(A_{1j}=a_1,A_{2j}=a_2,S_{1j}=s_1,S_{2j}=s_2)}{\sum_{i=1}^{n}Z_iI(A_{1i}=a_1,A_{2i}=a_2,S_{1i}=s_1,S_{2i}=s_2)+\sum_{j=1}^{m}I(A_{1j}=a_1,A_{2j}=a_2,S_{1j}=s_1,S_{2j}=s_2)}.$$

The asymptotic variance is similar to before by re-defining $\pi_k(a_1,a_2,s)$ as $\pi_k(a_1,a_2,s_1,s_2)$ through conditioning on both the baseline covariates S_1 and intermediate outcome S_2. That is,

$$\begin{aligned}V &\equiv Var_s\left(Z\frac{I(A_1=d_1(S_1),A_2=d_2(S_1,A_1,S_2))}{p(A_1|S_1)p(A_2|S_1,A_1,S_2)}\right.\\ &\times\left\{(Y-\mu(d_1,d_2))+\frac{1-\alpha(A_1,S_1,S_2)}{\alpha(A_1,S_1,S_2)+\beta r(A_1,S_1,S_2)}(Y-E[Y|A_1,A_2,S_1,S_2])\right\}\\ &\left.+(1-Z)\frac{I(A_1=d_1(S_1))}{p(A_1|S_1)}E[Y-\mu(d_1,d_2)|A_1,A_2=d_2(S_1,A_2,S_2),S_1]\right)\\ &+\beta Var_e\left(\frac{(1-\alpha(A_1,S_1,S_2))\,(Y-E[Y|A_1,A_2,S_1,S_2])}{\alpha(A_1,S)+\beta r(A_1,S_1,S_2)}\frac{I(A_1=d_1(S_1),A_2=d_2(S_1,A_1,S_2))}{p(A_1|S_1)p(A_2|S_1,A_1,S_2)}\right).\end{aligned}$$

3. Design Efficiency of SMARTer

In this section, we study the efficiency gain or loss of the proposed design as compared to a SMART with no dropout. For simplicity of illustration, we assume $P(Z=1|A_1,S)$ to be a constant, i.e., $\alpha(a_1,s)=\alpha$, and let $\omega(s)=r(d_1(s),s)$. Furthermore, we denote $p(d_1(s)|s)=p_1(s)$ and $p(d_2(s,d_1(s))|d_1(s),s)=p_2(s)$, so the variance of $\widehat{\mu}(d_1,d_2)$ is V/n with

$$\begin{aligned} V &= E_s\left[\left(\frac{\alpha}{p_1(S)p_2(S)}+\frac{1-\alpha}{p_1(S)}\right)(\nu(S)-\mu(d_1,d_2))^2\right] \\ &\quad +E_s\left[\frac{\sigma(S)^2}{p_1(S)p_2(S)}\frac{\alpha(1+\beta\omega(S))^2+\beta(1-\alpha)^2\omega(S)}{(\alpha+\beta\omega(S))^2}\right], \end{aligned}$$

where $E_s[\cdot]$ is the expectation with respect to S in the SMART population,

$$\nu(s) = E_s(Y|A_1 = d_1(s), A_2 = d_2(d_1(s), s), S = s) = E_e(Y|A_1 = d_1(s), A_2 = d_2(d_1(s), s), S = s),$$

$$\text{and } \sigma(s)^2 = Var_s(Y|A_1 = d_1(s), A_2 = d_2(d_1(s), s), S = s)$$

$$= Var_e(Y|A_1 = d_1(s), A_2 = d_2(d_1(s), s), S = s).$$

When $\alpha = 1$, i.e., no participant drops out from SMART, V reduces to

$$V_0 = E_s\left[\frac{(\nu(S)-\mu(d_1,d_2))^2+\sigma(S)^2}{p_1(S)p_2(S)}\right],$$

which is the variance formula given in Murphy (2005) for SMART. Therefore, to measure the efficiency gain of the proposed design over SMART design without dropouts, we define relative efficiency $\rho = V_0/V$, where $\rho > 1$ implies the propose enrichment design is more efficient than the original SMART without dropout.

To further gain insights on efficiency comparison, we consider a special situation when treatment randomization does not depend on tailoring variables, i.e., $p_1(S) = p_1, p_2(S) = p_2$. We also assume that the enrichment population is close to the original SMART population so $\omega(s) \approx 1$, and let the ratio of within- and between-strata variance to be $\gamma \approx \sigma(s)^2/(\nu(s) - \mu(d_1, d_2))^2$. Let α denote the completion (non-dropout) rate, and $\beta = m/n$ denote the enrichment rate. We can show that

$$\rho \approx \frac{1+\gamma}{1-(1-\alpha)(1-p_2)+\gamma\frac{\alpha(1+\beta)^2+\beta(1-\alpha)^2}{(\alpha+\beta)^2}}. \tag{2}$$

From (2), the relative efficiency depends on randomization probabilities, within- and between-strata (S) variability and distribution ratios between the enrichment and SMART populations. Note that $\rho > 1$ implies the proposed SMARTER is more efficient than a SMART

without enrichment and no dropout. From the expression of ρ, we thus conclude:

(1) When $\alpha = 1$, there is no dropout after the first stage in SMARTER, our estimator reduces to be the same as the estimator in Murphy (2005), and thus $\rho = 1$.

(2) When $\alpha = 0$, that is, all subjects drop out after the first stage, $\rho \approx (1+\gamma)/(p_2 + \gamma/\beta)$. There is efficiency gain if $\beta > \gamma/(1+\gamma-p_2)$. More specifically, there is always efficiency gain if $\beta > 1$. Note that this is the extreme case in the sense that all subjects drop out and we synthesize two independent randomized trials on the two stages.

(3) For any $0 < \alpha < 1$, if $\alpha(1+\beta)^2 + \beta(1-\alpha)^2 \leqslant (\alpha+\beta)^2$, $\rho > 1$ implies efficiency gain. Particularly, the latter condition holds if we choose $\beta \geqslant 1$.

Figure 2 is the contour plot of ρ as a function of completion (non-dropout) rate α and the enrichment rate $\beta = m/n$ under $\gamma = 0.5, 2$, where each line represents the contour line of the marked relative efficiency ρ as defined above. For example, for the $\rho = 0.9$ line, $\alpha = 0.6$ corresponds to $\beta = 0.5$. That is, at 60% completion rate, a study needs to enrich 50% sample to obtain a SMARTER estimator with variance $1/0.9 \approx 1.11$ times the variance of SMART estimator with the same initial sample size but no dropout. Similarly, at the same completion rate, to achieve the same efficiency, β needs to be above 0.75; and to achieve a relative efficiency of $\rho = 1.1$, β need to be above 1.05. Note that the line with equal efficiency has a slow change rate indicating the increase of enrichment sample size is not sensitive to completion rate. The contour lines above the equal efficiency line ($\rho = 1$) are convex and increasing, indicating with lower dropout rate after the first stage, SMARTER requires more enrichment patients at the second stage to achieve higher efficiency than a SMART with no dropout. The opposite can be seen from the contour lines below the equal efficiency line which are concave and decreasing: with lower dropout rate, SMARTER requires less enrichment patients or no enrichment to achieve efficiency slightly lower than a SMART with no dropout.

[Figure 2 about here.]

Another way to understand the design efficiency of SMARTER is through sample size calculation for comparing two DTRs in a SMARTER study. We denote the difference in the mean outcome value as $\Delta\mu$ and assume the type I error rate of a two-sided test is 0.05 and 80% power to detect a difference. In the above simplified setting, the total sample size of SMARTER is $8(z_{0.05/2}+z_{0.2})^2\frac{\sigma^2(\bar{d}_2)}{(\Delta\mu)^2}$, where $\sigma^2(\bar{d}_2) = var(Y|\bar{A}_2 = \bar{d}_2)$, and z_q represents the q-th upper quantile of a standard normal distribution. With a completion rate of α, the sample size of SMART inflates to $8(z_{0.05/2} + z_\beta)^2\frac{\sigma^2(\bar{d}_2)}{\alpha(\Delta\mu)^2}$ to ensure sufficient power at the end of the second stage. For two DTRs with different first stage treatments, i.e., $d_1(S) \neq d_1'(S)$ for any S, one can compute the variance of the difference as $V(\bar{d}_2, \bar{d}_2') = V(\bar{d}_2) + V(\bar{d}_2')$. Assuming $\sigma^2(\bar{d}_2) = \sigma^2(\bar{d}_2')$, then ρ is also the ratio of variance of SMART and SMARTER estimator for comparing two DTRs. Thus the sample size of initial recruitment (n) for a SMARTER is $8(z_{0.05/2} + z_\beta)^2\frac{\sigma^2}{(\Delta\mu)^2\rho}$ to achieve the same efficiency. Table 1 provides the sample sizes for a SMARTER with an initial sample of n subjects and an enrichment sample of m subjects to achieve the same efficiency as a SMART recruiting 100 subjects and in an ideal case of no dropout. For example, if 40% patients drop out after the first stage randomization of SMARTER and the within- and between- stratum variance ratio $\gamma = 1$, Table 1 provides three combinations of initial stage and enrichment sample sizes for SMARTER to achieve the same efficiency: $(109, 54)$, $(80, 80)$ and $(62, 124)$. In contrast, when accounting for dropouts at the design stage for a SMART without enrichment, one needs 100/0.6=250 subjects.

4. Simulation Studies

Simulations results are based on 1000 replications of samples with initial enrollment of $n =$ 800 patients. They demonstrate the consistency and comparative efficiency of SMARTER compared with SMART under various scenarios with or without intermediate outcomes.

4.1 *Simulation Results without Intermediate Outcomes*

Here we assume there are two stages each with 2 candidate treatments, A_1 and A_2, and a randomization probability of 1/2. The baseline covariate S_1 takes random integer values $(0, 1, 2)$ with probabilities $(1/3, 1/3, 1/3)$. Let $S_2 = A_1(1 - S_1)$, and the final outcome after the second stage is $Y = S_2 + A_2(1-S_1) + I(S_1 = 1, A_1 = 1, A_2 = -1) + e$, where $e \sim \mathcal{N}(0, 1)$. The optimal dynamic rules for this setting are $d_1(S_1) = 2I(S_1 < 2) - 1$ and $d_2(S_1, A_1) = 2I(S_1 < 1) - 1$. Under this rule $\nu(S_1 = 0) = 2, \nu(S_1 = 1) = 1, \nu(S_1 = 2) = 2$, thus the optimal rule has a value of $\mu(d_1, d_2) = 1.667$. We consider two levels of completion rates $\alpha = 0, 0.5$, three levels of enrichment proportions $\beta = 0.5, 1, 2$ and two scenarios for the m enrichment patients with the baseline distribution of $q = (1/2, 1/4, 1/4)$ for S_1: scenario 1 simulates the distribution of A_1 for the enrichment patients the same as initially recruited patients, i.e., $q(A_1|S_1) = p(A_1|S_1) = 1/2$; and scenario 2 simulates different observed A_1 distribution $q(A_1 = 1|S_1) = 1/(1 + \exp(-0.5(2I(S_1 < 2) - 1)))$, that is, the enrichment patients are more likely to receive the optimal first-stage treatment.

Table 3 presents SMARTer estimators of a single DTR and comparison of two DTRs, as well as their efficiency gain (ρ) compared with SMART without dropout. We provide the estimates for the optimal treatment regime $d_1(S_1) = 2I(S_1 < 2) - 1$ and $d_2(S_1, A_1) = 2I(S_1 < 1) - 1$, and its comparison with an one-size-fits-all regime, $d_1'(S_1, A_1) = -1$ and $d_2'(S_1, A_1) = 1$, for which the mean outcome is $\mu' = 0$.

The results show the accuracy of the variance estimation and the simplified formula (2) of comparative efficiency. When all patients drop out ($\alpha = 0$), the relative efficiency ρ increases from about 0.5 to 2 when the enrichment size m increases from 0.5 to 2 times the original sample size n; when half of patients drop out ($\alpha = 0.5$), the relative efficiency ρ increases from about 0.9 to 1.3. As β increases, SMARTer is more efficient comparing to SMART design even when all patients drops out after the initial randomization ($\alpha = 0$) and SMARTer

combines two single-stage randomized trials. We also observe that the relative efficiency ρ for comparing two DTRs is greater (more efficient) than estimating a single DTR.

4.2 *Simulation Results with Intermediate Outcomes*

The general settings are the same with section 5.1. The intermediate outcome before the second stage treatment S_2 is simulated from a logistic model, where $\text{logit}\{P(S_2 = 1|A_1, S_1)\} = A_1(1 - S_1)$, and the outcome after the second stage treatment is $Y = S_2 + A_2(1 - X) + I(X = 1)A_2(2S_2 - 1) + e$, where $e \sim \mathcal{N}(0, 1)$. The dynamic rules we are considering is the optimal rule under this scenario, which also depends on the intermediate outcome S_2: $d_1(S_1, A_1) = 2I(S_1 = 1)-1$ and $d_2(S_1) = I(S_1 \neq 1)(2I(S_1 = 0)-1)+I(S_1 = 1)\text{sign}(2S_2-1)$. Under this rule $\nu(S_1 = 0) = 1 + \frac{e}{1+e}, \nu(S_1 = 1) = 1.5, \nu(S_1 = 2) = 1 + \frac{e}{1+e}$. Thus the mean outcome for the optimal rule is $\mu(d_1, d_2) = 1.654$ with equal baseline distribution for S_1.

Table 3 presents SMARTER estimators of both a single DTR and comparison of two DTRs, as well as their efficiency gain (ρ) compared with SMART estimator with no dropout. We present the estimates for the optimal DTR and its comparison with an one-size-fits-all rule: $d_1'(S_1, A_1) = -1$ and $d_2'(S_1, A_1, S_2) = 1$, for which the mean outcome is $\mu' = 0.5$. The true mean difference is 1.154. The results are similar to the case without intermediate outcome. When $\beta = 1$, $\hat{\rho}$ is approximately equal or larger than 1, and it is higher for the difference comparison in Table 4. We observe that SMARTER estimator has efficiency gain even with $\beta = 1$ and it may boost efficiency especially when comparing two DTRs.

5. Sample size calculation for an Autism SMART study

We illustrate the sample size calculation and potential efficiency gain using results from the autism study (Kasari et al., 2014) introduced in Section 2.1. For the primary aim, they study found that SGD(JASP+EMT+SGD) has a better treatment effect compared with spoken words alone (JASP+EMT). Secondary aim results suggest that the adaptive intervention

beginning with JASP+EMT+SGD and intensifying JASP+EMT+SGD for children who were slow responders led to better post-treatment outcomes.

Suppose we stratify by baseline variables and responding status (early or slow) after the first stage. Here we provide the sample size calculation for comparing two adaptive treatment regimes as in the secondary study aim: one is starting with JASP+EMT+SGD and intensifying JASP+EMT+SGD for children who are slow responders ($\bar{d}_2$); the other is starting with JASP+EMT, and the slow-responders to JASP+EMT receive JASP+EMT+SGD ($\bar{d}_2'$).

The original planned sample size was based on the primary aim to compare TSCU for two treatments in stage 1. The study assumed an attrition rate of 10% by week 24, and the planned total sample size was $n = 97$ to detect a moderate effect size of 0.6 in TSCU with 80% power using a two-sided two-sample t-test with a type I error rate of 5%. The actual study recruited 61 patients. The effect size for the primary aim comparison was 0.62 and it was significant at 0.05 level despite the insufficient power. As a secondary aim of the study, the effect size of the embedded DTRs $\bar{d}_2$ and $\bar{d}_2'$ for TSCU at week 24 was 0.55. There were approximately 15% patients dropped out after the first stage at week 12. The comparison of two DTRs in the secondary aim had approximately a power of 37% to detect a moderate effect size of 0.5.

We examine whether one can design a SMARTer to enrich the trial in the second stage so that the power for comparing two DTRs can be improved. To this end, note the following holds $Z_\beta \leqslant \frac{\Delta\mu}{\eta/n}$, where $\Delta\mu$ is the effect size, and $\eta = (V(\bar{d}_2) + V(\bar{d}_2'))/\sigma^2 = \frac{4+0.8\alpha}{\gamma+1} + \frac{4.8\gamma}{1+\gamma}\frac{1+\alpha\beta}{\alpha+\beta}$. When $\gamma = 0.5$, we have $Z_\beta \leqslant -0.115$ and we can achieve at most 55% in power by enrichment in the second stage. To achieve 80% power, one needs to at least recruit 151 patients in the first stage.

Table 2 provides sample sizes for SMARTer and SMART that achieve the same power of 90%, 85% or 80% for two-sided tests with a type I error rate of 5%. The sample size for initial

stage of SMARTER is computed by $n = \frac{(2+2\times0.6+4\times0.4)(Z_{\alpha/2}+Z_{\beta})^2}{\Delta\mu^2}$, where we take into account $\bar{d}_2$ was randomized only in the first stage and for $\bar{d}'_2$, only the 40% slow responders received two-stages of randomization. The enrichment ratio β is computed by solving $V(\bar{d}_2)+V(\bar{d}'_2) = V_0(\bar{d}_2)+V(\bar{d}'_2)$ (by independence of subjects following $\bar{d}_2$ and $\bar{d}'_2$), that is, to solve the following equation $\frac{1}{1+\gamma}(2+2(1-\alpha)+(2\times0.6+4\times0.4)\alpha)+\frac{\gamma}{1+\gamma}(2+2.8)\frac{1+\alpha\beta}{\alpha+\beta} = 2+2.8$. The solution is $\beta = \frac{6\gamma-\alpha}{6\gamma+1}$.

Since we do not have information on the ratio of within and between stratum variances γ, we provide results for three ratios $\gamma = 0.2, 0.5, 1$ and also two rates of attrition 15% and 40% after the first stage. According to Table 2, for this specific example, SMARTER would have smaller total sample size for initial recruitment and enrichment when γ is small ($\gamma = 0.2$) with attrition rate 15% and for $\gamma = 0.5$ with attrition rate 40%. SMARTER would be more beneficial for smaller sample sizes and when both groups being compared receive two stages of randomization.

6. Discussion

We propose a SMARTER design to improve efficiency over SMART by enriching study participants at each stage of a multi-stage trial. We have shown that the new design retains the validity of making causal inference for DTRs and the efficiency gain is significant if drop out rate is considerable and the enrichment sample size is substantial. In all numeral results, we compared efficiency of SMARTER to SMART with no dropout. When comparing with SMART accounting for dropouts, the efficiency gain is expected to be greater than that shown here. One interesting application of SMARTER design is the extreme case when $\alpha = 0$, so the proposed design is equivalent to synthesizing different independent trials from each stage. One important implication is that if the conditions (C.1)–(C.4) hold, i.e., the treatment response profiles are the same for the participants from each stage and the

treatment history in previous stages of the enrichment sample can be obtained, then we no longer need to conduct a full SMART in order to evaluate DTRs. Therefore, in practice, it may be possible to synthesize existing trials conducted at separate stages to compare DTRs, at least for the purpose of discovering optimal DTRs. At the other extreme, when there is no attrition (i.e., $\alpha = 1$) SMARTER can still be used to gain efficiency by replacing Y_i in $\widehat{\mu}(d_1, d_2)$ by the corresponding stratum mean estimated from the combined SMART and enrichment sample, which is less variable.

Data collected from the SMARTER can also be used to find optimal DTR using methods such as Q-learning (Murphy et al., 2007; Watkins, 1989). Using a two-stage design as an example, first one can find the optimal second stage treatment using the subjects randomized at the second stage, which includes n_1 group 1 subjects and the m group 3 enrichment subjects. Next, one can use the regression model in Q-learning from this step to predict the optimal outcomes of the group 2 dropout subjects and identify optimal second stage treatment. Lastly, group 1 and 2 subjects are used to estimate the optimal treatment rule for the first stage. More details on how to estimate the optimal rule and a simulation study are included in the Web Appendix B.

Unmeasured confounding may be a concern in statistical inference using enrichment group observational data. However, note that the enrichment sample is only used to predict outcomes for those who drop out from the original SMART group randomized for the first stage treatments. The enrichment samples are not directly included in the comparisons of the DTRs. The second stage treatment options for enrichment sample are randomized and they are matched with the SMART group based on health information collected right before second stage randomization (including intermediate outcomes). Thus under the assumption (C.2) of missing at random and assumption (C.3) of the same conditional distribution given health information up to stage 2, valid inference can be drawn by predicting SMART drop out

subjects using enrichment sample. When dropout patterns are complicated and depend on many intermediate outcomes, our simple estimation by stratification and matching may need to be improved. A straightforward modification is instead of matching on all stratification variables, select enrichment sample with matched cumulative summaries of main variables (e.g., same number of interim outcome measures). Other model based methods or doubly robust estimation may be considered for more complex situations especially when auxiliary variables are available for estimating missingness.

From the real data example in Section 6, we see that although enrichment can improve the power for comparing DTRs, the maximal power one can attain still depends on the sample size in the first stage recruitment. Recruiting an enrichment sample can decrease the within-stratum variation but can not decrease the variation from between-stratum variation. Therefore, in reality practitioners may design a SMART with a sample size assuming a small drop out after the first stage, and consider enriching the study sample at the second stage to achieve the predetermined power if the actual observed dropout rate is high during the first stage of treatment. In this case, SMARTer may act as a salvage design to mitigate high drop out rate. In addition, one major reason for the low participation rate in clinical trials and high attrition is the need for frequent in-person visits and the resulting time and travel costs (Ross et al., 1999), which can be reduced for the enrichment samples in SMARTer since these participants have already received first stage treatments. For the enrichment sample, the cost of monitoring first stage treatment is saved, and the duration of trial for this group can be considerably less than recruiting patients in the first stage to under go multiple randomizations. The chance to retain participants in the trial can be much higher.

Finally, from a design point of view, although we allow the distribution of first-stage treatment history and covariates on the enrichment participants to be different from the SMART population, the more similar they are, the more efficiency we will gain by using the

enrichment participants. This implies that when recruiting enrichment patients for the second stage treatments, similar inclusion/exclusion criteria as SMART may be used and certain sampling design may be implemented to improve matching. Furthermore, since SMARTer requires the treatment responses between the enrichment and SMART population to have the same distributions, caution should be taken when one suspects that the two populations may have different response mechanisms to treatments. Sensitivity analysis can be conducted in the analysis phase.

7. Web Appendix

In the web appendix, we provide derivation of the asymptotic variance of the estimator for expected outcome under a given DTR, as well as description and preliminary simulation results for learning the optimal DTR from SMARTer.

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[Table 1 about here.]

[Table 2 about here.]

[Table 3 about here.]

[Table 4 about here.]

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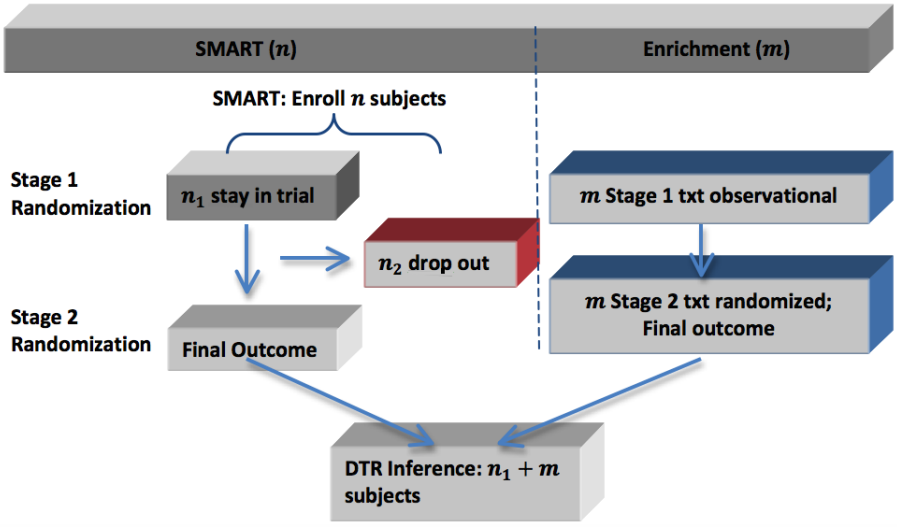

Figure 1: Diagram of SMARTER Design

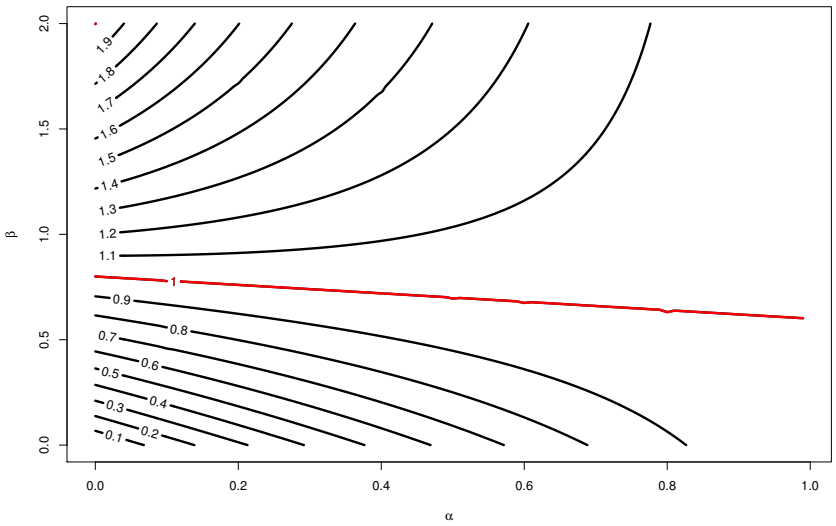

Figure 2: Contour Plot of Comparative Efficiency of SMARTER and SMART. α is the completion rate, β is the sample size ratio between enrichment group and original SMART group.

Table 1: Sample sizes of SMARTER to achieve the same efficiency as SMART with 100 subjects for comparing two DTRs with different first stage treatments

α	0		.2		.4		.5		.6		.8	
SMARTER*			$\beta = 0.5$									
	n	m	n	m	n	m	n	m	n	m	n	m
$\gamma = 0.5$	100	50	92	46	91	46	92	46	93	46	96	48
$\gamma = 1$	125	62	109	54	102	51	100	50	99	50	99	49
$\gamma = 2$	150	75	125	62	112	56	108	54	105	53	102	51
			$\beta = 1$									
$\gamma = 0.5$	67	67	73	73	80	80	83	83	87	87	93	93
$\gamma = 1$	75	75	80	80	85	85	88	88	90	90	95	95
$\gamma = 2$	83	83	87	87	90	90	92	92	93	93	97	97
			$\beta = 2$									
$\gamma = 0.5$	50	100	61	122	72	143	77	153	82	163	91	182
$\gamma = 1$	50	100	62	124	73	145	78	155	82	165	91	183
$\gamma = 2$	50	100	62	125	73	147	78	157	83	166	92	184
SMART-mis†	NA		500		250		200		167		125	

*: Sample sizes for SMARTER are to achieve same efficiency as a SMART trial with 100 patients and in an ideal case of no dropout. n is the sample size for the SMART group, m is the sample size for the enrichment group; $\beta = m/n$ is the ratio of sample size between enrichment and SMART group; α is the completion rate; γ is ratio of within- and between-stratum variance.

†: SMART-mis is the sample size for a SMART accounting for the dropout rate of $1 - \alpha$ in the second stage in the design, i.e., $100/\alpha$.

Table 2: Sample sizes of SMARTer to achieve the same efficiency as SMART for the Autism Study

	Dropout Rate	Power 90%			Power 85%			Power 80%		
		SMART	SMARTer		SMART	SMARTer		SMART	SMARTer	
			n	m		n	m		n	m
$\gamma = 0.2$	0%	202	202	0	173	173	0	151	151	0
	15%	238	202	27	203	173	15	178	151	18
	40%	337	202	54	288	173	43	252	151	40
$\gamma = 0.5$	0%	202	202	0	173	173	0	151	151	0
	15%	238	202	104	203	173	81	178	151	76
	40%	337	202	120	288	173	100	252	151	89
$\gamma = 1$	0%	202	202	0	173	173	0	151	151	0
	15%	238	202	144	203	173	117	178	151	106
	40%	337	202	155	288	173	130	252	151	115

Sample sizes for SMARTer are to achieve same power as a SMART trial with the same initial recruitment as n and in an ideal case of no dropout. n is the sample size for the SMART group, m is the sample size for the enrichment group; γ is ratio of within- and between-stratum variance.

Table 3: Results from the simulation study without intermediate outcomes

α	β	Scenario	Estimate	Estimated SE	empirical SD	95% CI coverage	$\widehat{\rho}$
				Value estimation of one DTR			
0.0	0.5	1	1.667	0.115	0.111	0.910	0.527
		2	1.660	0.123	0.109	0.937	0.546
	1.0	1	1.668	0.083	0.080	0.936	1.019
		2	1.664	0.088	0.075	0.940	1.151
	2.0	1	1.668	0.061	0.057	0.933	1.975
		2	1.667	0.065	0.057	0.938	1.969
0.5	0.5	1	1.665	0.085	0.084	0.953	0.891
		2	1.662	0.085	0.083	0.948	0.905
	1.0	1	1.665	0.077	0.078	0.945	1.039
		2	1.665	0.077	0.077	0.943	1.048
	2.0	1	1.664	0.070	0.070	0.949	1.284
		2	1.664	0.071	0.070	0.949	1.300
				Comparing two different DTRs†			
0.0	0.5	1	1.669	0.161	0.156	0.911	0.497
		2	1.661	0.173	0.154	0.930	0.504
	1	1	1.668	0.115	0.111	0.925	0.971
		2	1.665	0.122	0.111	0.929	0.978
	2	1	1.669	0.083	0.077	0.929	2.026
		2	1.665	0.088	0.078	0.944	1.987
0.5	0.5	1	1.669	0.116	0.117	0.950	0.818
		2	1.665	0.117	0.115	0.954	0.852
	1	1	1.668	0.105	0.107	0.944	0.979
		2	1.669	0.107	0.106	0.949	1.000
	2	1	1.666	0.095	0.096	0.953	1.231
		2	1.666	0.096	0.096	0.951	1.225

Note: α represents probability of non-dropout; $\beta = m/n$; ρ is the relative efficiency using the formula in Section 4, and $\widehat{\rho}$ is the empirical efficiency; scenario 1: the enrichment population has distritubiton $q = (1/2, 1/4, 1/4)$ for $(0, 1, 2)$, and $q(A_1|S_1) = 1/2$; scenario 2: $q = (1/2, 1/4, 1/4)$ and observed treatment A_1 distribution $q(A_1 = 1|S_1) = 1/(1 + exp(-0.5(2I(S_1 < 2) - 1)))$

†: Efficiency ρ is the same for estimating one DTR and comparing two DTRs with different first stage treatments

Table 4: Results from the simulation study with intermediate outcomes

α	β	Scenario	Estimate	Estimated SE	empirical SD	95% CI coverage	$\widehat{\rho}$
				Value estimation of one DTR			
0.0	0.5	1.0	1.653	0.114	0.112	0.903	0.527
		2.0	1.651	0.127	0.113	0.929	0.519
	1.0	1.0	1.655	0.083	0.079	0.923	1.007
		2.0	1.654	0.092	0.082	0.944	0.936
	2.0	1.0	1.657	0.061	0.058	0.926	1.915
		2.0	1.654	0.067	0.060	0.950	1.758
0.5	0.5	1.0	1.653	0.084	0.084	0.948	0.896
		2.0	1.653	0.085	0.084	0.952	0.887
	1.0	1.0	1.655	0.077	0.074	0.958	1.127
		2.0	1.655	0.078	0.075	0.956	1.113
	2.0	1.0	1.653	0.070	0.072	0.945	1.240
		2.0	1.653	0.071	0.071	0.944	1.245
				Comparing two different DTRs			
0	0.5	1	1.158	0.172	0.147	0.945	0.733
		2	1.155	0.177	0.147	0.950	0.735
	1	1	1.154	0.127	0.109	0.954	1.258
		2	1.152	0.130	0.106	0.963	1.319
	2	1	1.157	0.096	0.083	0.959	2.287
		2	1.150	0.098	0.083	0.963	2.280
0.5	0.5	1	1.159	0.124	0.124	0.941	1.018
		2	1.158	0.124	0.124	0.939	1.032
	1	1	1.155	0.115	0.114	0.947	1.150
		2	1.156	0.116	0.114	0.946	1.150
	2	1	1.152	0.107	0.104	0.960	1.394
		2	1.153	0.108	0.105	0.953	1.367

Note: See Table 1.