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COBRA Preprint Series

Year 2010 *Paper* 69

Efficient Design and Inference for Multi-stage Randomized Trials of Individualized Treatment Policies

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Abstract

Increased clinical interest in individualized 'adaptive' treatment policies has shifted the methodological focus for their development from the analysis of naturalistically observed strategies to experimental evaluation of a pre-selected set of strategies via multi-stage designs. Because multi-stage studies often avoid the 'curse of dimensionality' inherent in uncontrolled studies, and hence the need to parametrically smooth trial data, it is not surprising in this context to find direct connections among different methodological approaches. We show by asymptotic and algebraic proof that the maximum likelihood (ML) and optimal semi-parametric estimators of the mean of a treatment policy and its standard error are equal under certain experimental conditions. The two methodologies offer conceptually different formulations, which we exploit to develop a unified and efficient approach to design and inference for multi-stage trials of policies that adapt treatment according to discrete responses. We derive a sample size formula expressed in terms of a parametric (regression-based) version of the optimal semi-parametric population variance. Non-parametric (sample-based) ML estimation performed well in simulation studies, in terms of achieved power, even though sample sizes relied on parametric re-expression. For a variety of simulated scenarios, ML outperformed the semi-parametric approach, which used a priori rather than estimated randomization probabilities, because the test statistic was sensitive to even small differences arising in finite samples.

1. Introduction

Increased clinical interest in individualized treatment policies has shifted the methodological focus for their development from the analysis of 'naturalistically' observed strategies (Murphy et al. 2001; Hernan et al. 2006) to experimental evaluation of a pre-selected set of strategies via multi-stage designs (Lavori and Dawson, 2000; Thall et al., 2000; Lunceford et al., 2002). The candidate policies under evaluation have been described as 'adaptive' treatment strategies (ATS) or 'dynamic' treatment regimes (Lavori and Dawson 2008) because treatment changes are tailored to the circumstances of the individual, including response to prior treatments. The studies have been described as sequential, multiple assignment, randomized (SMAR) trials (Murphy 2005) because successive courses of treatment are randomly and adaptively assigned over time, according to the individual subject's treatment and response history. The multiple stages of randomization correspond to the sequential decision making formalized by an ATS, the primary goal of the trial being to evaluate entire strategies, rather than stage-specific treatment options.

A typifying example of an adaptive treatment strategy occurs in the treatment of a chronic disorder such as depression. The following ATS exemplifies the decision algorithm used in the SMAR trial of antidepressants known as STAR*D (Rush et al. 2004): 'Start on A; after a sufficient medication trial, switch to *B* if response is poor or side effects persist, otherwise either continue on *A* or augment *A* with *C*, depending on the degree of improvement; continue to monitor and augment or switch to treatments *D* and *F*, respectively, according to degree of response.' As in STAR*D, the SMAR design specifies that all subjects in the trial start on *A*, so that the first randomization is to possible treatment options for *B* and *C* , which is nested within the response categories for treatment with *A*. For example, subjects who experience side effects are randomized to one of the alternatives for B. Further randomization to options for

D and F is similarly nested within previous treatment and response history. Subjects who respond well enough to A and continue to do so are never randomized, but participate fully in all stages of the trial.

Clinical equipoise successively guides SMAR treatment options for B,C, D and F, just as it guides fixed treatment alternatives in single-stage trials (Dawson and Lavori 2010). That principle, coupled with standardizing of clinical details (e.g., dosing, duration of medication trial), reduces the typically explosive variation in treatment regimes found in observational settings (Lavori and Dawson 2004). Because SMAR studies often avoid the 'curse of dimensionality' inherent in uncontrolled studies, and hence the need to parametrically smooth trial data, it is not surprising in this context to find direct connections among different methodological approaches. This paper shows that the simplest estimators of the population mean of an ATS and its standard error, derived using probability calculus and 'plug-in' method of moments estimates, are equal under certain experimental conditions to the analogous estimators provided by optimal semi-parametric theory, maximum likelihood (ML) theory, and Bayesian predictive inference. In particular, we assume that constrained randomization (e.g., sequential blocking) insures that the observed allocation of subjects matches that intended by design (Dawson and Lavori 2008). We also assume that the specification of the ATS and the choice of SMAR sample size insure 'replete' datasets at the end of the experiment, in the sense of precluding random zeroes at intermediate randomization steps (Lavori and Dawson 2007).

The equality of the optimal variance estimator with the others is not obvious by appearance and full induction across randomization stages is required to derive the result algebraically. The different formulations for standard error clarify how the distinct methodological perspectives complement each other. The iterative probability calculus (also underlying ML and predictive estimators) is carried out sequentially according to the nested structure of SMAR data, to reflect the influence due to intervening outcomes used for multi-stage

randomization. The resulting variance estimator decomposes into stage-specific components corresponding to the uncertainty associated with estimating the conditional distributions of successive outcomes. In this way, it quantifies the inference 'penalty' paid at each SMAR stage for not knowing *a priori* the population parameters for their joint distribution. By contrast, the efficient semi-parametric influence function used to obtain the optimal variance estimator is a 'marginal' mean model for the outcome measured at the end of the study (Murphy et al. 2001). The resulting variance estimator derives from the population marginal variance of the final outcome, typically used for determining sample size in single-stage trials, plus a sum of stage-specific variances of the inversely weighted final outcome.

In this paper, we exploit the marginal character of the semi-parametric approach to derive a regression-based formula suitable for sample size calculations, which minimizes reliance on unknown population parameters and is expressed in quantities familiar to the trialist. We also derive a non-parametric counterpart for the semi-parametric efficiency gains provided by the optimal estimator, relative to the simpler marginal mean estimator defined by Murphy for SMAR trials (2005). We consider the performance of ML and semi-parametric inference, in terms of achieved power, when using the regression-based sample size formula. The intent is to provide a unified and efficient approach to design and inference for SMAR trials of ATS that adapt treatment according to discrete responses.

2. Design Framework and Estimators

Consider a SMAR trial with *K* stages of randomization. The multi-stage design can be described sequentially in terms of the adaptive randomized treatment assignments. Let S_1 be the (observed) baseline state of the subject, taking values denoted by $s_{1,}$ and let A_1 be initial treatment assigned as a function of $s_{1,}$

taking values denoted by a_1. Analogously for stage *k* in 2, … , *K* let S_k be the status of the subject measured at the start of the k^{th} stage and A_k the treatment assigned by the k^{th} randomization according to values for $\boldsymbol{S}_k$ and $\boldsymbol{A}_{k\text{-}1}$, where $\boldsymbol{S}_k = (S_1, S_2, \ldots, S_k)$ and $\boldsymbol{A}_{k\text{-}1} = (A_1, A_2, \ldots, A_{k\text{-}1})$. SMAR assignment to different treatment options can be expressed in terms of (sequential) allocation to different decision rules, each of which determines treatment as a function of the current and past states and past treatments. Formally, we write $a_k = d_k(\boldsymbol{S}_k = \boldsymbol{s}_k, \boldsymbol{A}_{k\text{-}1} = \boldsymbol{a}_{k\text{-}1})$ for the decision rule d_k at the k^{th} stage; the randomization probabilities for d_k, denoted $\{p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1})\}$, are known and experimentally fixed functions of prior state-treatment history.

The (observable) strategies to be evaluated from the multi-stage design can be represented as sequences of the SMAR decision rules with positive probability of assignment. Specifically, each SMAR sequence $\{d_1, d_2, \ldots, d_K\}$ corresponds to an ATS, which we denote as $\boldsymbol{d}$, if the domain for each successive rule includes the state-treatment histories produced by previous rules in the sequence. This condition insures that the *K*-stage ATS is a well-defined policy for adaptively determining the 'next' treatment. The introductory example consists of two decision rules $\{d_1, d_2\}$, given that all subjects in the SMAR trial start on *A* : $A \equiv a_{1(1)} = d_1(S_1 = 1)$, $A+C \equiv a_{1(2)} = d_1(S_1 = 2)$ and $B \equiv a_{1(3)} = d_1(S_1 = 3)$, where the baseline state S_1 indicates response to *A*. The second decision rule is similarly defined. For example, $a_1 \equiv a_{2(1,1)} = d_2(S_2 = 1, a_1)$, where S_2 indicates response measured after the first randomization. The more cumbersome notation, such as $a_{2(1,1)}$, makes explicit that treatment is a function of prior state-treatment history.

The SMAR design includes a primary outcome *Y*, obtained after the K^{th} stage of randomization, which is used for evaluation purposes. We judge the

performance of an ATS $\boldsymbol{d}$ by $\mu_{\boldsymbol{d}}$, the population mean of Y that would be observed if all subjects were treated according to $\boldsymbol{d}$.

2.1 Estimator of the Mean of an ATS

Previously, we derived a method of moments estimator of $\mu_{\boldsymbol{d}}$ from SMAR trial data using iterated expectation and showed that under certain experimental conditions, it is equal to the marginal mean (MM) estimator defined by Murphy for SMAR trials (Lavori and Dawson 2007). Specifically, the two estimators are the same when at any given stage k, the proportion of subjects with state-treatment history $(\boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1})$ randomized to $\boldsymbol{d}$ coincides with the assignment probability $p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1})$. Such coincidence occurs asymptotically by the law of large numbers and might be achieved in a study using sequentially blocked randomization. When this holds, both estimators of $\mu_{\boldsymbol{d}}$ can be expressed in terms of stage-specific, stratified sample quantities as:

$$\sum_{\boldsymbol{s}_K} \phi_K(\boldsymbol{s}_K) m_K(\boldsymbol{s}_K) \tag{1}$$

where $m_K(\boldsymbol{s}_K)$ is the sample mean of final responses among subjects sequentially randomized to $\boldsymbol{d}$ through K and having state values $\boldsymbol{S}_K = \boldsymbol{s}_K$,

$$\phi_K(\boldsymbol{s}_K) = \prod_{k=1}^{K} f_k(\boldsymbol{s}_k) \tag{2}$$

and $f_k(\boldsymbol{s}_k)$ is the sample (conditional) response rate for $S_k = s_k$, given assignment to $\boldsymbol{d}$ through k-1 and $\boldsymbol{S}_{k\text{-}1} = \boldsymbol{s}_{k\text{-}1}$. The estimator (1) is a version of the non-parametric G-computational formula (Robins 1989) and is suitable for strategies that adapt treatment according to discrete states, such as the ATS in

the Introduction. Under the assumption of sequential ignorability (guaranteed by multi-stage randomization), (1) is consistent for $\mu_{\boldsymbol{d}}$.

Murphy et al. (2001) derived a semi-parametric estimator of $\mu_{\boldsymbol{d}}$, deemed optimal because it has the smallest variance among the class of all regular asymptotically linear (RAL) estimators. Let

$$D_k = \prod_{j=1}^{k} I(A_j = d_j(\boldsymbol{S}_j, \boldsymbol{A}_{j\text{-}1}))$$

indicate assignment to strategy $\boldsymbol{d}$ through stage k, where $I(B)$ is 1 if B occurs, otherwise 0, and let

$$P_k(\boldsymbol{s}_k) = \prod_{j=1}^{k} p_j(d_j | \boldsymbol{S}_j, \boldsymbol{A}_{j\text{-}1})$$

be the probability of being sequentially randomized through k to $\boldsymbol{d}$ given $\boldsymbol{S}_k = \boldsymbol{s}_k$. The optimal estimator is obtained by solving the efficient estimating equation $\frac{1}{n}\sum U_{opt} = 0$, where n is the number of subjects and U_{opt} is defined as:

$$U_{opt}(\boldsymbol{S}_K, \boldsymbol{d}_K, \boldsymbol{\mu}_K, \mu_{\boldsymbol{d}}) = D_K P_K^{-1}(\boldsymbol{s}_K)\{Y - \mu_K(\boldsymbol{s}_K, \boldsymbol{d}_{K\text{-}1})\} \qquad (3)$$

$$+ \sum_{k=1}^{K\text{-}1} D_k P_k^{-1}(\boldsymbol{s}_k)\{\mu_{k+1}(\boldsymbol{s}_{k+1}, \boldsymbol{d}_k) - \mu_k(\boldsymbol{s}_k, \boldsymbol{d}_{k\text{-}1})\}$$

$$+ \{\mu_1(s_1) - \mu_{\boldsymbol{d}}\}$$

with $\mu_k(\boldsymbol{s}_k, \boldsymbol{d}_{k\text{-}1}) = E(Y_{\boldsymbol{d}} | \boldsymbol{S}_k = \boldsymbol{s}_k, \boldsymbol{A}_{k\text{-}1} = \boldsymbol{d}_{k\text{-}1})$ for k in 1,...,K; $Y_{\boldsymbol{d}}$ denotes the primary outcome when the subject is treated according to strategy $\boldsymbol{d}$. Note that for $k = 1$, $\mu_k(\boldsymbol{s}_k, \boldsymbol{d}_{k\text{-}1}) \equiv \mu_1(s_1)$.

The G-computational formula (1) can be used to provide consistent non-parametric estimates of the μ_k (given SMAR randomization), in which case, the solution to the estimated estimating equation is optimal (Murphy et al. 2001). It also reduces to (1). This follows because all but the last term of U_{opt} are zero when the G-estimates for μ_k are 'plugged' into (3); solving the last term of the estimating equation (using the plug-in G-estimate) leads to (1). The result holds asymptotically without restriction, but otherwise requires that the observed allocation of subjects matches that intended by design, as noted above for the MM estimator. This condition is required because U_{opt} uses assignment probabilities for inverse weighting, whereas sample estimates in (1) use the observed assignment proportions. Unless stated otherwise, we assume blocking or some other form of constrained randomization makes this distinction moot for analytic derivations, and use the notation $p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1})$ interchangeably for expected and observed proportions under strategy $\boldsymbol{d}$, as well as $P_k(\boldsymbol{s}_k)$ for their cumulative products.

Because the ML estimates for means and proportions coincide with the 'plug-in' estimates obtained by the method of moments, (1) is also ML. It is also equal to the predictive estimator of $\mu_{\boldsymbol{d}}$, assuming non-informative priors (Dawson and Lavori 2008). We therefore refer to (1) unambiguously as the estimator of the ATS mean, denoted $\hat{\mu}_{\boldsymbol{d}}$.

2.2 Variance Estimators of the Estimator of the Mean of an ATS

To obtain the asymptotic ML variance of $\hat{\mu}_{\boldsymbol{d}}$, we assume (i) the final outcome Y has a stratified normal distribution across strata indexed by the possible sequences $(\boldsymbol{s}_K, \boldsymbol{a}_K)$, (ii) the intermediate states S_k are distributed conditionally, given $(\boldsymbol{s}_k, \boldsymbol{a}_k)$, as multinomial random variables, (iii) model parameters are distinct across state-treatment histories for a given stage k and across stages. Because the sequence of nested randomizations in a SMAR trial gives rise to a monotone pattern of missingness for each ATS, the likelihood can be factored into distinct components, each of which is a complete-data problem. Standard theory dictates that the (asymptotic) ML variance, obtained from the information matrix, is block diagonal, with each block corresponding to a complete-data component. It is possible to derive the ML variance from the information matrix for the parameters in the factored form of the likelihood, inverting, and then transforming back to the original (joint) parameterization. However, a more tractable derivation calculates the ML variance directly using iterated variance decomposition (Little and Rubin 1987). For the SMAR set up, the iterated calculation mimics that used to sequentially identify $\mu_{\boldsymbol{d}}$, and produces the same variance estimator previously obtained using probability calculus coupled with the method of moments (Lavori and Dawson 2007) or Bayesian predictive inference (Dawson and Lavori 2008). We use $\hat{v}_{ML}$ to denote the variance estimator of $\hat{\mu}_{\boldsymbol{d}}$ provided by these three derivations.

The expression for $\hat{v}_{ML}$ established using iterated decomposition has two primary components: the 'naïve' variance estimate that assumes the coefficients of $m_K(\boldsymbol{s}_K)$ in (1) are known *a priori*, denoted $\hat{v}_n$, and the 'penalty' paid for estimating them via (2), denoted $\hat{v}_p$:

$$\hat{v}_{ML} = \hat{v}_n + \hat{v}_p$$

where (suppressing dependence on state history)

$$\hat{v}_n = \sum_{\boldsymbol{s}_K} \phi_K^2 \hat{\mathrm{v}}(m_K); \qquad \hat{v}_p = \sum_{\boldsymbol{s}_K, \boldsymbol{s}'_K} m_K m'_K \hat{\mathrm{cov}}(\phi_K, \phi'_K); \tag{4}$$

and $\hat{\mathrm{v}}(m_K) \equiv \hat{\mathrm{v}}(m_K(\boldsymbol{s}_K))$ is the sample variance of $m_K(\boldsymbol{s}_K)$ and $\phi'_K \equiv \phi_K(\boldsymbol{s}'_K)$ (Dawson and Lavori 2008). The estimated covariances $\hat{\mathrm{cov}}(\phi_K, \phi'_K)$ can be obtained by induction on k, with the cross-sectional case K =1 being the usual multinomial calculation (Lavori and Dawson 2007). For general K, there is a component of 'penalty' variance for each stage due to estimating the conditional distributions of S_k indexed by state history. The k^{th}-stage term of $\hat{\mathrm{cov}}(\phi_K, \phi'_K)$ fixed at $\boldsymbol{s}_{k\text{-}1}$ can be directly expressed in terms of the large sample variance and covariances of the estimated proportions $f_k(\boldsymbol{s}_{k\text{-}1}, s_k)$, $f_k(\boldsymbol{s}_{k\text{-}1}, s'_k)$ defined for (2); see the Appendix.

The estimated asymptotic variance of the optimal semi-parametric estimator of $\mu_{\boldsymbol{d}}$, denoted $\hat{v}_{OPT}$, is obtained non-parametrically from the variance of U_{opt} (Murphy 2005). Specifically, $\hat{v}_{OPT}$ is the estimate of $\frac{1}{n}\mathrm{V}(U_{opt})$, where

$$\mathrm{V}(U_{opt}) = E_{\boldsymbol{d}}(Y - \mu_{\boldsymbol{d}})^2 + \sum_{k=1}^{K} E_{\boldsymbol{d}}[(1 - p_k) P_k^{-1} (Y - \mu_k)^2] \tag{5}$$

and the expectation $E_{\boldsymbol{d}}()$ is calculated under the distribution of $\boldsymbol{S}_K$ and Y when all treatments are assigned according to the strategy $\boldsymbol{d}$. As before, the μ_k are estimated using the G-computational formula, which guarantees that $\hat{v}_{OPT}$ achieves the semi-parametric efficiency bound (Murphy et al. 2001).

To show equality of the asymptotic ML and optimal semi-parametric variance estimators, we posit that Y takes on only a finite number of possible values, and reframe the normal model (i) as multinomial. Given sufficiently large n, either specification will give nearly the same sample estimates of mean and variance required for ML estimation (Rubin 1987). Hence, the assumed likelihood model for $\mu_{\boldsymbol{d}}$ can be taken as non-parametric for practical problems, such as those arising in the type of SMAR trials considered here. We also note that the semi-parametric efficiency bound for $\mu_{\boldsymbol{d}}$, which is equal to $\hat{v}_{OPT}$, is the same whether or not the randomization probabilities (the 'nuisance' parameters) are known (Bickel et al. 1993). Therefore, for our purposes, it suffices to consider the semi-parametric model corresponding to the 'true' non-parametric model for $\mu_{\boldsymbol{d}}$, and fixed at the parameter values for the randomization probabilities (Robins and Ritov 1997). Standard theory implies that the semi-parametric bound is at least as large as the asymptotic ML variance of $\hat{\mu}_{\boldsymbol{d}}$, so that $\hat{v}_{ML} \leq \hat{v}_{OPT}$. Moreover, because the optimal estimator of $\mu_{\boldsymbol{d}}$ is assumed equal to the ML estimator of $\mu_{\boldsymbol{d}}$, given large samples or constrained randomization, it follows directly that the asymptotic semi-parametric efficiency bound for $\mu_{\boldsymbol{d}}$ is equal to the Cramer Rao bound for $\mu_{\boldsymbol{d}}$ or equivalently $\hat{v}_{ML}$ (Tsiatis 2006), thereby establishing equality. An immediate consequence of this result is that the simulation studies previously carried out for ML estimators (actually their method of moments and predictive counterparts) pertain to $\hat{v}_{OPT}$. Those studies demonstrate that the estimators have good finite sample coverage for the SMAR trials considered here (Lavori and Dawson 2007; Dawson and Lavori 2008).

It is also possible to use induction to algebraically show equality of the variance estimators (see the Appendix). The result demonstrates that the normality of the likelihood has no impact on the above proof that $\hat{v}_{ML} = \hat{v}_{OPT}$. A key element of the inductive proof is the ANOVA decomposition:

$$\hat{v}_{OPT} = \hat{v}_n + \frac{1}{n}\{ \sum_{\boldsymbol{s}_K} \phi_K (m_K - \hat{\mu}_{\boldsymbol{d}})^2 + \sum_{k=1}^{K-1} \hat{e}_{\boldsymbol{d}}[(1-p_k)P_k^{-1}(m_K - \hat{\mu}_k)^2] \} \quad (6)$$

where $\hat{e}_{\boldsymbol{d}}()$ is the sample estimator of $E_{\boldsymbol{d}}()$ obtained via inverse weighting:

$$\hat{e}_{\boldsymbol{d}}(h(Y)) = \sum_{i=1}^{n} D_{K,i} P_{K,i}^{-1} h(Y_i) \quad (7)$$

.

(As before, we suppress extra notation whenever possible.) Algebraic re-expression of the $(m_K - \hat{\mu}_k)^2$ in (6) in terms of covariances provides a direct comparison of $\hat{v}_{OPT} - \hat{v}_n$ to the 'penalty' component of $\hat{v}_{ML}$, defined in (4). As shown in the Appendix, the k^{th}-stage covariances derived from $\hat{v}_{OPT} - \hat{v}_n$ are standard (K = 1) large sample multinomial covariances of the 'pseudo' proportions $p = \prod_{j=k}^{K} f_j$ and $p' = \prod_{j=k}^{K} f'_j$. As described above, the k^{th}-stage term of $\hat{v}_p$ restricts covariance uncertainty to f_k and f'_k. Accordingly, the difference $\hat{v}_{ML} - \hat{v}_{OPT}$ gives rise to K remainder terms. An inductive argument establishes overall equality of the variance estimators by showing that the successive remainders telescope to zero.

3. Optimal Semi-parametric Variance for Sample Size Calculations

For the purposes of developing sample size formulae for inference for $\mu_{\boldsymbol{d}}$, we can choose either formulation of the variance estimator for $\hat{\mu}_{\boldsymbol{d}}$. Here, we exploit the marginal character of the semi-parametric approach and re-express $\mathrm{V}(U_{opt})$ in terms of regression quantities that would be familiar to the trialist. To do so,

we assume that $E_{\boldsymbol{d}}[(Y-\mu_k)^2 \mid \boldsymbol{s}_{\boldsymbol{d},k}] = V_{\boldsymbol{d}}(Y \mid \boldsymbol{s}_{\boldsymbol{d},k}) = \sigma_k^2(\boldsymbol{s}_{\boldsymbol{d},k})$ is homogeneous across state history at *k*, i.e., $\sigma_k^2(\boldsymbol{s}_{\boldsymbol{d},k}) \equiv \sigma_{k,\boldsymbol{d}}^2 \equiv \sigma_k^2$. Applying iterated expectation to the stage k term in (5) yields:

$$E_{\boldsymbol{d}}[(1-p_k)P_k^{-1}(Y-\mu_k)^2] = E_{\boldsymbol{d}}[E_{\boldsymbol{d}}[(1-p_k)P_k^{-1}(Y-\mu_k)^2 \mid \boldsymbol{s}_{\boldsymbol{d},k}]] \quad (8a)$$

$$= E_{\boldsymbol{d}}[(1-p_k)P_k^{-1}]\sigma_k^2 \quad (8b)$$

Furthermore, $E_{\boldsymbol{d}}[(1-p_k)P_k^{-1}] = (1-p_k)P_k^{-1}$ if the k^{th}-stage randomization probabilities are all equal to $p_k(d_k)$. In this case, $\mathrm{V}(U_{opt})$ is re-expressed as:

$$\sigma_Y^2 + \sum_{k=1}^{K}(1-p_k)P_k^{-1}\sigma_k^2 \quad (9)$$

where $\sigma_{Y,\boldsymbol{d}}^2 \equiv \sigma_Y^2$ is the marginal variance of $Y_{\boldsymbol{d}}$. Let $R_T^2 = (1-\sigma_K^2/\sigma_Y^2)$ be the coefficient of determination for the regression of $Y_{\boldsymbol{d}}$ on $\boldsymbol{S}_{\boldsymbol{d},K}$, and R_k^2 denote the (population) increment in coefficient of determination when $S_{\boldsymbol{d},k}$ is added to the regression of $Y_{\boldsymbol{d}}$ on $\boldsymbol{S}_{\boldsymbol{d},k-1}$. Then (9) becomes:

$$\sigma_Y^2 P_K^{-1}[1-(1-P_K)R_1^2 - (1-P_K p_1^{-1})R_2^2 - \ldots - (1-p_K)R_K^2] \quad (10)$$

noting that $R_T^2 = \sum R_k^2$. We refer to the multiplier of σ_Y^2 as the 'variance inflation factor' (VIF) due to the SMAR design, which generalizes to:

$$E_{\boldsymbol{d}}(P_K^{-1}) - E_{\boldsymbol{d}}[(1-P_K)P_K^{-1}]R_1^2 - E_{\boldsymbol{d}}[(1-P_K p_1^{-1})P_K^{-1}]R_2^2 - E_{\boldsymbol{d}}[(1-p_K)P_K^{-1}]R_K^2 \quad (11)$$

when randomization probabilities depend on prior state values.

Using either (10) or (11) as appropriate provides the SMAR version of the usual one-sample t-test formula for sample size:

$$(z_{\alpha/2} + z_{\beta})^2 \frac{\text{VIF}}{\text{ES}^2} \qquad (12)$$

where α is the significance level, 1- β is the power to be achieved, and ES = $(\mu_{\boldsymbol{d}} - \mu_0)/\sigma_Y$ is the standardized difference between $\mu_{\boldsymbol{d}}$ and the null mean. The formula (12) assumes a two-sided test of the null hypothesis that $\mu_{\boldsymbol{d}} = \mu_0$, and the (approximate) large sample normality of the semi-parametric estimator. Note that the sample size calculation does not require any assumptions for the unknown distribution of the $\boldsymbol{S}_{\boldsymbol{d},K}$ when $p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1}) \equiv p_k(d_k)$ for all k. This would occur when subjects are allocated with equal probability to treatment alternatives, which themselves are equal in number at every decision point of a particular stage.

The formula (12) extends in a straightforward way to sample size calculations for inference for pairs of ATS, using pooled values for VIF and σ_Y^2. However, the pooled version of (12) does not address the possible role of between-strategy covariance in causal inference. Such covariance arises in a SMAR trial because of the nested structure of the randomizations. Dawson and Lavori (2010) use the regression quantities in (12) to provide an adjustment to SMAR sample size when covariance is substantial enough to increase efficiency.

4. Semi-parametric Efficiency Gains with the Optimal Estimator

Murphy (2005) obtains the simple MM estimator of $\mu_{\boldsymbol{d}}$ and its standard error by setting each μ_k in U_{opt} to $\mu_{\boldsymbol{d}}$. To characterize the potential loss of efficiency in doing so, we express the variance of the MM estimator of $\mu_{\boldsymbol{d}}$, denoted $\hat{v}_{MM}$, in ANOVA form as:

$$\hat{v}_{MM} = \hat{v}_n + \hat{v}_b; \qquad \hat{v}_b = \frac{1}{n}\sum_{\boldsymbol{s}_K} \phi_K P_K^{-1}(m_K - \hat{\mu}_{\boldsymbol{d}})^2 \tag{13}$$

with $\hat{v}_b$ accounting for response heterogeneity across subgroups indexed by state history (Lavori and Dawson 2007) .

. We compare (13) to $\hat{v}_{OPT}$, as expressed in (6). With some algebra, it follows from (7) that:

$$\frac{1}{n}\hat{e}_{\boldsymbol{d}}[P_k^{-1}(m_K - \hat{\mu}_k)^2] = \frac{1}{n^2}\sum_{\boldsymbol{s}_K} P_K^{-1} P_k^{-1} n_K (m_K - \hat{\mu}_k)^2 \tag{14}$$

and

$$\hat{v}_{OPT} = \hat{v}_n + \sum_{\boldsymbol{s}_K} P_K \hat{\mathrm{v}}_b(\boldsymbol{s}_K) + \frac{1}{n}\sum_{k=1}^{K-1}\sum_{\boldsymbol{s}_K}(1 - p_k) P_k^{-1}\phi_K (m_K - \mu_k)^2 \tag{15}$$

where $\hat{\mathrm{v}}_b(\boldsymbol{s}_K)$ is the summand of $\hat{\mathrm{v}}_b$ corresponding to $\boldsymbol{s}_K$. Thus, the optimal variance estimator improves semi-parametric efficiency, in part, by downweighting $\hat{\mathrm{v}}_b$.

To further characterize efficiency gains, consider $\hat{v}_b$ and the term of (15) corresponding to k. Define Δ_k as:

$$\Delta_k = \sum_{\boldsymbol{s}_K} \phi_K (m_K - \hat{\mu}_{\boldsymbol{d}})^2 - \sum_{\boldsymbol{s}_K} \phi_K (m_K - \hat{\mu}_k)^2 \tag{16}$$

which can be re-expressed as:

$$\Delta_k = \; = \sum_{\boldsymbol{s}_k} \phi_k \hat{\mu}_k^2 - \hat{\mu}_{\boldsymbol{d}}^2 \tag{17}$$

noting that $\hat{\mu}_k = \sum_{(s_{k+1},\ldots,s_K)} \phi_K \phi_k^{-1} m_K$. Suppose that S_k is binary (always achievable by introducing more stages), taking on values s_k , s_k' . Accordingly, Δ_k can be sequentially defined in terms of stage-specific response heterogeneity $\Delta_k = \delta_k + \delta_{k-1} \ldots + \delta_2 + \delta_1$, where

-

$$\delta_k = \sum_{\boldsymbol{s}_{k-1}} \phi_{k-1} f_k f_k' \{\hat{\mu}_k(\boldsymbol{s}_{k-1}, s_k) - \hat{\mu}_k(\boldsymbol{s}_{k-1}, s_k')\}^2; \qquad \delta_1 = \Delta_1 \tag{18}$$

and $f_k' = f_k(\boldsymbol{s}_{k-1}, s_k') = 1 - f_k(\boldsymbol{s}_{k-1}, s_k) \equiv 1 - f_k$. The derivation follows by induction.

We can re-express $\hat{v}_{OPT} - \hat{v}_{MM}$ directly in terms of the δ_k when $p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k-1}) \equiv p_k(d_k)$ for all k. The case $K = 3$ suffices to concretely explicate the general result:

.

$$\hat{v}_{OPT} = \hat{v}_n + p_3 \hat{v}_b - p_3(1-p_1p_2)\delta_1 - p_3(1-p_2)\delta_2 \tag{19a}$$

$$= \hat{v}_{MM} - (1-p_3)\hat{v}_b - p_3(1-p_1p_2)\delta_1 - p_3(1-p_2)\delta_2 \tag{19b}$$

The SMAR randomization probabilities, which are specified *a priori* by the trialist, govern increased semi-parametric efficiency provided by the optimal estimator, and do so in a simple way under the assumed restrictions. The strength of the relationship of state history to Y, as evidenced by the magnitudes of the δ_k , has impact as well, with $\hat{v}_{OPT} = \hat{v}_{MM}$ when there is no between-subgroup response heterogeneity at any stage of the stud y.

Simple differentiation of (19) shows that efficiency gains for the assumed SMAR set up are maximized (as a function of state history) when each S_k acts like a flip of a fair coin, thereby allowing sequential allocation of subjects to each possible state history. The worst improvement occurs when at each stage but the last, S_k is a degenerate binomial, i.e., all mass on one outcome. This makes intuitive sense if you consider that this scenario isn't adaptive until the last stage, and is formally equivalent to the cross-sectional K = 1 case.

5. Simulation Studies

A central issue to the sample size formula (12) is how well the parametric re-expression of $\mathrm{V}(U_{opt})$, derived using the assumption of homogeneity of variance, adequately matches non-parametric inference carried out using the estimators in Section 2. It may be that successive stratification leads to one or more random zeroes at intermediate stages of randomization, even if the nominal level of power is achieved (in the frequency sense). As the sample size grows, the chance of this diminishes. We conducted simulations to understand the degree to which good performance of the sample size formula across repeated samples protects the trialist from an unlucky SMAR realization. Because (12) may also fail to protect against near sampling zeroes (and thereby interfere with constrained randomization), we calculated the test statistic twice, using ML and semi-parametric estimators.

The simulation set up is designed to explicate the relationship between 'repleteness', defined as the lack of random zeroes at any intermediate stage of the SMAR experiment, and calculated sample size. Data for the example ATS, described in the Introduction and denoted here as $\boldsymbol{d}$, are generated by the following scheme. The state space at each stage is {1,2,3}, which corresponds to "low, medium, or high" symptoms; these values determine whether to adaptively continue, augment or switch medication, using the stage-specific treatments specified by $\boldsymbol{d}$. As in the STAR*D antidepressant study, baseline state is obtained after an initial trial on the medication A. The S_1 values are set to be equiprobable. The values for $S_{\boldsymbol{d},2}$ are produced according to the transition matrix TM with rows (0.7, 0.2, 0.1), (0.5, 0.3, 0.2), (0.1,0.5,0.4), where TM_{ij} = $\Pr(j|i)$. The matrix TM is consistent with "healthier" subjects having greater probability of better successive outcomes. The final outcome is generated as a regression on state history, with normal error: $Y_{\boldsymbol{d}} = \boldsymbol{S}_{\boldsymbol{d},2}{}^{T}\beta + e$, $e \sim \mathrm{N}(0, \sigma_e^2)$, where (β_1, β_2) = (1.2) and the intercept β_0 = 0.5 is the coefficient for $S_0 \equiv 1$.

The randomization probabilities for assignment to $\boldsymbol{d}$ depend on prior state values: subjects who are (well, in partial remission, ill) continue on $\boldsymbol{d}$ with probability (1, 1/3, 1/2). The values for the randomization probabilities are also suitable for generally investigating semi-parametric efficiency gains with the optimal estimator, because the analytic derivation required $p_k(d_k | \boldsymbol{S}_k, \boldsymbol{A}_{k\text{-}1}) \equiv p_k(d_k)$ for all k. For purposes of inference for $\mu_{\boldsymbol{d}}$ (generated to be 6.10), we set the standardized effect size in the formula (12) to be either 0.2 or 0.4. The trialist might specify the larger ES value to insure adequate precision for individual ATS means when planning a pilot SMAR trial. The inherent 'cost' in successfully implementing a whole treatment strategy makes it unlikely that the trialist would find effects smaller than 0.2 of practical relevance.

We note that an alternative version of the simulation set up described above was used to evaluate (12) for pairwise comparisons, and more generally for sizing a SMAR trial with equal randomization probabilities, with particular attention to the role played by between-strategy covariance (Dawson and Lavori 2010). To explicitly allow for simulated causal effects due to the final treatment A_K (for a K-stage trial), that set up included a 'final' state $S_{\boldsymbol{d},K+1}$, not necessarily measured during a real trial, which was part of state history used to generate $Y_{\boldsymbol{d}}$. For our context, including $S_{\boldsymbol{d},3}$ in the simulation substantially increases the chance of a non-replete SMAR experiment in a way that would not occur in practice. Because we do not have interest here in the use of (12) for causal inference, there is no reason to disallow the 'null' effect of final treatment.

6. Results

Table 1 summarizes 2000 replications for every combination of ES = 0.2, 0.4 and σ_e = 0.5, 1, 2. Scenarios also varied by whether the simulated trial used a 'safe' mechanism to guarantee positive sample sizes across state histories at both stages of the simulated trial (Lavori and Dawson 2007). Specially, 'safe' implies that once the number of subjects for a particular state history falls below a certain value (set here to 6), further randomization stops and subjects with those states continue on $\boldsymbol{d}$ thereafter. The 'safe' mechanism is intended to reflect the effects of good practice, in the sense that the trialist would ensure repleteness, either through design or by monitoring subject accrual during the trial. For all scenarios, randomized assignment was sequentially constrained via blocking to insure whenever possible that observed and expected allocations agreed. Throughout, the nominal level of power to be achieved was set to 0.80, with the level of the test = 0.05. The test statistic, defined as the difference of the estimated mean and the null value divided by the standard error, was compared

to 1.96, suggested by asymptotic normality of the ML and semi-parametric estimators of μ_d .

The results show that when ES = 0.2, the calculated sample sizes insure repleteness for all but a very small number of experiments. By contrast, when ES = 0.40, the proportion of replete experiments among the 2000 replications ranges from 60% to 89%. One could argue that for most SMAR trials, the primary interest will be to detect moderate-sized causal effects, thereby increasing the sample size beyond that provided by (12) when ES = 0.4. Nonetheless, the simulations serve to illustrate the relevance of repleteness to good planning of a SMAR experiment, beyond the usual sample size considerations.

A more striking result in Table 1 is the differences in power achieved by the ML and optimal semi-parametric estimators. The ML estimators are mostly robust to even substantial failures of repleteness, because of their use of sample quantities in (1) and (4) based on allocated proportions. In contrast, the semi-parametric reliance on assignment probabilities precludes the optimal estimator from tuning to the sample at hand, which may not be able to attain intended allocation proportions, due to sequential stratification of the sample across stages. This is true even with mostly replete repetitions, highlighting the influence of near sampling zeroes on achieved power with semi-parametric estimation. It is not surprising that the optimal estimator may sometimes be underpowered when the simulated trials use the 'safe' option, given that certain *a priori* randomization probabilities may be set to zero. It is interesting that ML estimation insures nominal power under the 'safe' option, albeit conservatively for some scenarios. This property makes it a suitable choice for inference, prior to the execution of the trial, and any knowledge of the stochastic process underling intermediate states. This 'self-tuning' property of ML estimation in the face of random and near sampling zeroes reminds us that the (asymptotically derived) ML variance estimator coincides with the finite sample one obtained from the

method of moments. We note that for practical purposes, the ML and semi-parametric estimators of $\mu_{\boldsymbol{d}}$ and its standard error show mostly minor differences. This is expected, as the discrepancies across subgroup of subjects, stratified by state history, would tend to average out because the discrepancies reflect random chance. However, the test statistic is a ratio, and can be sensitive to even small changes to its divisor.

Table 2 shows that repleteness and near sampling zeroes have a moderate impact on the semi-parametric efficiency gains provided by the optimal estimator, which entails estimation of the μ_k in U_{opt} using inverse weights. In theory, such gains should not depend on n, and simulations with excessively large sample sizes show this to be the case. In the designed simulations carried out with realistic values for n, the relative efficiency for any given value of σ_e depended on whether the sample size was geared to ES = 0.2 or ES = 0.4. Nonetheless, the results of the simulations confirm that the strength of the relationship of state history to $Y_{\boldsymbol{d}}$, as evidenced by the R_T^2 values, governs the magnitude of efficiency gains.

6. Discussion

In this paper, we have shown by asymptotic and algebraic proof that the ML and optimal semi-parametric estimators of $\mu_{\boldsymbol{d}}$ and its standard error are equal under certain experimental conditions. The two methodologies offer conceptually different formulations, which we exploit to develop a unified and efficient approach to design and inference for multi-stage SMAR trials with discrete intermediate states. By applying a sequential version of the homogeneity of variance assumption often used for power calculations, we derived a sample size formula expressed in terms of a parametric (regression-based) version of the optimal semi-parametric population variance. Our simulation studies show that

for finite samples, non-parametric (sample-based) ML estimation achieves nominal power across repeated experiments when randomization is sequentially constrained, even if some of those repetitions are not replete or suffer from near sampling zeroes. In this sense, ML estimation offers 'frequentist-based' protection against near population zeroes, which the semi-parametric does not provide. Moreover, it offers protection for the sample at hand, by providing at least nominal power when the trial design includes a 'safe' mechanism that selectively shuts down randomization when the number of subjects at a decision point falls below some minimum. This makes ML estimation a suitable *a priori* choice for inference. We note that the advantage of using observed rather than expected allocation proportions, exemplified by the simulation results for achieved power, has been discussed for studies with non-randomized treatments or missing data in terms of bias and efficiency (Rosenbaum 1987, Rotnizky and Robins 1995).

The sample and population formulations of semi-parametric variance developed in this paper elucidate the central role played by response heterogeneity in determining the magnitude of sequential uncertainty. Section 4 offers a non-parametric characterization of sample response heterogeneity in terms of stage-specific between-subgroup sum of squares, which captures the sequential effect of response heterogeneity on semi-parametric efficiency. The increments in regression-based coefficients of determination defined in Section 3 provide the parametric counterparts at the population level, and analogously describe the sequential effect of response heterogeneity (via incremental strength of regression) on sample size requirements. Because even the optimal (or worst) strategy would not be uniformly successful (or not) across state history, both characterizations apply generally to ATS under evaluation.

Less apparent is the dual role played by response heterogeneity in SMAR trials and accordingly in estimators developed for their data structure. Not only does response heterogeneity govern sequential efficiency, but also the entire

premise of an adaptive treatment strategy rests with a strong relationship between outcome and state on which to base decisions. Because the SMAR design mimics sequential decision making, the missingness intentionally created by sequential (nested) randomization is governed implicitly by variation in responses across states for any given strategy. In the absence of such variation, treatment assignment at any given stage reduces to a flip of a fair coin, making sequential adjustment for state history, as in the G-computational formula, unnecessary. For certain estimators, such as the ML and optimal semi-parametric ones considered here, their adjustment for SMAR missingness to guarantee consistency also reaps the usual efficiency gains, as translated to the sequential context.

The framework developed here for ATS evaluation is appropriate when decisions are based on categorical symptom-based states, such as the clinical milestones (e.g., remit or not) used in managing chronic relapsing disorders (Rush et al. 2004) and rapidly fatal diseases (Thall et al. 2007). Bembom and van der Laan (2008) proposed a semi-parametric approach for the case when decisions are formalized as threshold rules based on continuous data, as might be appropriate for managing HIV/AIDS, and indicate extension to the optimal version would follow from standard theory. For semi-parametric estimation of survival distributions in two-stage induction-maintenance oncology trials, Wahed and Tsiatis (2004) derived the locally efficient influence function that capitalizes on the time to response to the induction therapy, as a continuous covariate. To date, sample size formulae have not been developed for the locally optimal case of Wahed and Tsiatis or the threshold designs of Bembom and van der Laan.

The results in this paper emphasize the importance of running a 'tight' trial, using sequentially constrained randomization in combination with some version of an *a priori* designated 'safe' option. The trialist should also consider whether the calculated sample size will sufficiently protect against sparse data, and whether a larger number of subjects might circumvent the need for a 'safe'

option, which effectively truncates the ATS under evaluation. The simulation set up provides one means to translate clinical judgments about intermediate response rates into the frequentist probability of experimental repleteness. The trialist can also use the simulation set up to 'firm up' guesses for variance inflation factors when plausible values for regression quantities are lacking.

Acknowledgements

Supported by National Institute of Mental Health Grant No. R01-MH51481 to Stanford University.

Appendix

Proof of equality of optimal semi-parametric and ML variance estimators

Claim 1: Let $\phi_{K|k} = \phi_K \phi_k^{-1}$. Then

$$\frac{1}{n}\hat{e}_{\boldsymbol{d}}[P_k^{-1}(m_K - \hat{\mu}_k)^2] = \sum_{\boldsymbol{s}_K, \boldsymbol{s}'_K} I(\boldsymbol{s}_k = \boldsymbol{s}'_k)\phi_k^2 m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_{K|k}, \phi'_{K|k}; n_k)$$

where $\mathrm{cov}_{\mathrm{F}}(p,p';n) = \frac{1}{n}\{I(s=s')p - pp'\}$, $\phi'_{K|k} = \phi_K(\boldsymbol{s}'_K)\phi_k^{-1}(\boldsymbol{s}'_k)$ and $n_k \equiv n_k(\boldsymbol{s}_k) = n\phi_k(\boldsymbol{s}_k)P_k(\boldsymbol{s}_k)$ is the number of subjects at stage k with state history $\boldsymbol{s}_k$.

Proof:

Let $\boldsymbol{s}_{k+1,\ldots,K} = (s_{k+1}, \ldots, s_K)$ be the last K-k values of the sequence $\boldsymbol{s}_K$ and

$$\hat{\mu}_k = \sum_{(s_{k+1},\ldots,s_K)} \phi_K \phi_k^{-1} m_K = \sum_{\boldsymbol{s}_{k+1,\ldots,K}} \phi_{K|k} m_K \qquad \text{(A.1)}$$

where $\hat{\mu}_k \equiv \hat{\mu}_k(\boldsymbol{s}_k)$ and the first k values of $\boldsymbol{s}_K$ (implied argument to ϕ_K and m_K) are fixed at $\boldsymbol{s}_k$. It follows from (7) and (A.1) that

$$\frac{1}{n}\hat{e}_{\boldsymbol{d}}[P_k^{-1}(m_K - \hat{\mu}_k)^2] = \frac{1}{n^2}\sum_{\boldsymbol{s}_K} P_K^{-1}P_k^{-1}n_K(m_K - \hat{\mu}_k)^2 \tag{A.2}$$

$$= \sum_{\boldsymbol{s}_k}\phi_k^2 n_k^{-1} \sum_{\boldsymbol{s}_{k+1,\ldots,K}} \phi_{K|k}(m_K - \hat{\mu}_k)^2 \tag{A.3}$$

$$= \sum_{\boldsymbol{s}_k}\phi_k^2 \sum_{\boldsymbol{s}_{k+1,..,K},\boldsymbol{s}'_{k+1,..,K}} m_K(\boldsymbol{s}_K)m_K(\boldsymbol{s}_k,\boldsymbol{s}'_{k+1,..,K})\mathrm{cov}_{\mathrm{F}}(\phi_{K|k}(\boldsymbol{s}_K),\phi_{K|k}(\boldsymbol{s}_k,\boldsymbol{s}'_{k+1,..,K});n_k) \tag{A.4}$$

$$= \sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K} I(\boldsymbol{s}_k = \boldsymbol{s}'_k)\phi_k^2 m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_{K|k},\phi'_{K|k};n_k) \tag{A.5}$$

(Note that $n_j = n\phi_j P_j$, $j = k, K$, and $\sum \phi_{K|k}(m_K - \hat{\mu}_k)^2 = [\sum \phi_{K|k} m_K^2] - \hat{\mu}_k^2$ given that the 'mixing' or weighting factor for $\hat{\mu}_k$ is $\phi_{K|k}$.) Hence, $\hat{v}_{OPT}$ can be expressed as:

$$\hat{v}_{OPT} = \hat{v}_n + \sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K} m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_K,\phi'_K;n) \tag{A.6}$$

$$+ \sum_{k=1}^{K-1}\sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K}(1 - p_k)I(\boldsymbol{s}_k = \boldsymbol{s}'_k)\phi_k^2 m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_{K|k},\phi'_{K|k};n_k) \tag{A.7}$$

using the ANOVA decomposition (6).

Claim 2: $\hat{v}_{OPT} = \hat{v}_{ML}$

Fix $\boldsymbol{s}_K, \boldsymbol{s}'_K$, and (suppressing dependence on $\boldsymbol{s}_K, \boldsymbol{s}'_K$ whenever possible) define stage-specific terms for $\hat{v}_{ML}$ and $\hat{v}_{OPT}$, respectively:

$$G_k = I(\boldsymbol{s}_{k-1} = \boldsymbol{s}'_{k-1})\phi^2_{k-1}\hat{\text{cov}}(f_k, f'_k)\phi_{K|k}\phi'_{K|k} \tag{A.8}$$

$$V_k = I(\boldsymbol{s}_{k-1} = \boldsymbol{s}'_{k-1})\phi^2_{k-1}\,\text{cov}_{\text{F}}(\phi_{K|k-1}, \phi'_{K|k-1}; n_{k-1}) \tag{A.9}$$

noting that the k^{th}-stage term of $\hat{\text{cov}}(\phi_K, \phi'_K)$ in (4) is:

$$I(\boldsymbol{s}_{k-1} = \boldsymbol{s}'_{k-1})\phi^2_{k-1}\hat{\text{cov}}(f_k, f'_k)\prod_{j=k+1}^{K} f_j \prod_{j=k+1}^{K} f'_j\,. \tag{5}$$

where $\hat{\text{cov}}(f_k, f'_k) = \frac{1}{n_{k-1}}\{I(s_k = s'_k)f_k - f_k f'_k\}$. (We ignore $m_K m'_K$, given conditioning on state history.) It follows directly from (A.7) that the difference $G_K - (1 - p_{K-1})V_K$ gives rise to a remainder $R_K = p_{K-1}V_K$.

Let $R_k = G_k - (1 - p_{k-1})V_k + R_{k+1}$ be the stage-k remainder, and consider $r_k = G_k - V_k + R_{k+1}$, $k < K$. Assume $R_{k+1} = p_k V_{k+1}$ (the inductive assumption). When $I(\boldsymbol{s}_k = \boldsymbol{s}'_k) = 0$, it follows trivially that $r_k = 0$, given that this implies $G_k = V_k$ (apply formula for covariance of distinct probabilities) and $R_{k+1} = 0$. When $I(\boldsymbol{s}_k = \boldsymbol{s}'_k) = 1$, we re-express p_k / n_k as $1/(n_{k-1}f_k)$, so that R_{k+1} becomes:

$$I(\boldsymbol{s}_k = \boldsymbol{s}'_k)\phi_{k-1}\phi_k \upsilon(\phi_{K|k}, \phi'_{K|k})/n_{k-1} \qquad \text{(A.10)}$$

where $\upsilon(p,p';n) = n\mathrm{cov}_{\mathrm{F}}(p,p';n)$. Assume further that $I(\boldsymbol{s}_K = \boldsymbol{s}'_K) = 0$. Then (ignoring the common factor $1/n_{k-1}$) $G_k - V_k + R_{k+1}$ becomes:

$$r_k = \{\phi_{k-1}\phi_K\phi'_{K|k} - \phi_K\phi'_K\} + \phi_K\phi'_K - \phi_{k-1}\phi_K\phi'_{K|k} = 0 \qquad \text{(A.11)}$$

noting that $\phi_k = \phi'_k$ and $f_k\,\phi_{k-1} = \phi_k$. For the remaining case, i.e., $I(\boldsymbol{s}_K = \boldsymbol{s}'_K) = 1$,

$$r_k = \{\phi_{k-1}\phi_K\phi_{K|k} - \phi_K\phi_K\} - \{\phi_K\phi_{k-1} - \phi_K\phi_K\} + \{\phi_K\phi_{k-1} - \phi_{k-1}\phi_K\phi_{K|k}\} = 0 \quad \text{(A.12)}$$

Hence, $R_k = p_{k-1}V_k$. By a similar argument, the final remainder:

$$\sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K} m_K m'_K \phi_{K|1}\phi'_{K|1}\hat{\mathrm{cov}}(\phi_1,\phi'_1) + \sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K} p_1 I(s_1 = s'_1)\phi_1^2 m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_{K|1},\phi'_{K|1};n_1)$$

$$- \sum_{\boldsymbol{s}_K,\boldsymbol{s}'_K} m_K m'_K \mathrm{cov}_{\mathrm{F}}(\phi_K,\phi'_K;n) \qquad \text{(A.13)}$$

Is equal to zero, thus establishing overall equality of two variance estimators. (Consider the cases determined by whether or not $s_1 = s'_1$ crossed with whether or not $\phi_{K|1} = \phi'_{K|1}$.)

References

Bembom, O., van der Laan, M.J. (2008). Analyzing sequentially randomized trials based on causal effect models for realistic individualized treatment rules. *Statistics in Medicine*, **27**, 3689-3716.

Bickel, P.J., Klaassen, C.A.J., Ritov, Y. and Wellner, J.A. (1993) *Efficient and adaptive estimation for semiparametric models.* Baltimore: John Hopkins University Press.

Dawson, R. and Lavori, P.W. (2008). Sequential causal inference: Application to randomized trials of adaptive treatment strategies. *Statistics in Medicine*, **27**, 1626-45.

Dawson, R. and Lavori, P.W. (2010). Sample Size Calculations for Evaluating Treatment Policies in Multi-stage Design. For consideration in *Clinical Trials*.

Hernán, M.A., Lanoy, E., Costagliola, D. and Robins, J.M. (2006) Comparison of dynamic treatment regimes via inverse probability weighting. *Basic & Clinical Pharmacology & Toxicology*, **98**, 237-242.

Lavori, P.W. and Dawson, R. (2000) A design for testing clinical strategies: biased adaptive within-subject randomization. *J. R. Statist. Soc. A.*, **163**, 29-38.

Lavori, P.W. and Dawson, R. (2004). Dynamic treatment regimes: practical design considerations. *Clinical Trials*, **1**, 9-20.

Lavori, P.W. and Dawson, R. (2007). Improving the efficiency of estimation in randomized trials of adaptive treatment strategies. *Clinical Trials*, **4**, 297-308.

Lavori, P.W. and Dawson, R. (2008). Adaptive treatment strategies in chronic disease. *Annual Review of Medicine*, **59**, 443-453.

Little, J.A. and Rubin, D.B. (1987) *Statistical Analysis with Missing Data*. New York: Wiley.

Lunceford, J.K., Davidian, M., and Tsiatis, A.A. (2002). Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics*, **58**, 48-57.

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

Murphy, S.M., van der Laan, M.J., and Robins, J.M. (2001). *Journal of the American Statistical Association*, **96**, 1410-1423.

Robins, J.M. (1989). The control of confounding by intermediate variables. *Statistics in Medicine*, **8**, 679-701.

Robins, J.M. and Ritov, Y.. (1997) Toward a curse of dimensionality appropriate (CODA) asymptotic theory for semi-parametric models. *Statistics in Medicine*, **16**, 285-319.

Rosenbaum, P.R. (1987) Model-based direct adjustment. *Journal of the American Statistical Association*, **82**, 387-394.

Rotnitzky, A. and Robins, J.R. (1995). "Semiparametric regression estimation in the presence of dependent censoring." *Biometrika*, **82**, 805-820.

Rubin, D.B. (1987) *Multiple Imputation for Non-response in Surveys*. New York: John Wiley.

Rush, A.J., Fava, M., Wisniewski, S.R., Lavori, P.W., Trivedi, M.H., Sackeim, H.A., et al (2004). Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin. Trials*, **25**, 119–142.

Thall, .P.F., Logothetis, C., Pagliaro, L.C., Wen, S., Brown, M.A., Williams, D. and Millikan, R. (2007) Adaptive therapy for androgen-independent prostate cancer: a randomized selection trial including four regimens . *J Natl Cancer Inst*., **99**, 1613 – 22 .

Thall, P.F, Millikan, R., and Sung, H-G. (2000). Evaluating multiple treatment courses in clinical trials. *Statistics in Medicine*, **19**, 1011-1028.

Tsiatis, A.A. *Semiparametric Theory and Missing Data*. (2006) New York: Springer.

Wahed, A.S., and Tsiatis, A.A. (2004). Optimal estimator for the survival distribution and related quantities for treatment policies in two-stage randomization designs in clinical trials. *Biometrics*, **60**, 124-133.

Table 1: Performance of Sample Size Formula for Nominal Power = 0.80 Using Either ML Estimation or Optimal Semi-parametric (SP) Estimation

σ_e^2	ES	Safe	VIF†	n‡	% Replete	Power: ML	Power: Optimal SP
0.5	**0.2**	**no**	1.62	320	99.3%	0.798	0.737
		yes	1.62	320	100%	0.798	0.756
	0.4	**no**	1.62	80	59.6%	0.818	0.664
		yes	1.62	80	100%	0.817	0.775
1.0	**0.2**	**no**	2.05	404	99.9%	0.803	0.768
		yes	2.05	404	100%	0.801	0.766
	0.4	**no**	2.05	101	72.2%	0.800	0.734
		yes	2.05	101	100%	0.849	0.826
2.0	**0.2**	**no**	2.97	587	100%	0.801	0.795
		yes	2.97	587	100%	0.792	0.784
	0.4	**no**	2.97	147	88.6%	0.803	0.780
		yes	2.97	147	100%	0.846	0.847

† Calculated from regression of $Y_{\boldsymbol{d}}$ on $\boldsymbol{S}_{\boldsymbol{d},2}$

‡Calculated using formula (12)

Table 2: Relative Efficiency of Optimal Semi-parametric Estimator to MM Semi-parametric Estimator

σ_e^2	ES	Safe	$R_T^{2\,\dagger}$	n‡	% Replete	$\hat{v}_{OPT}\ /\hat{v}_{MM}$
0.5	**0.2**	**no**	0.95	320	99.3%	0.425
		yes	0.95	320	100%	0.434
	0.4	**no**	0.95	80	59.6%	0.404
		yes	0.95	80	100%	0.626
1.0	**0.2**	**no**	0.81	404	99.9%	0.508
		yes	0.81	404	100%	0.511
	0.4	**no**	0.81	101	72.2%	0.460
		yes	0.81	101	100%	0.600
2.0	**0.2**	**no**	0.52	587	100%	0.687
		yes	0.52	587	100%	0.682
	0.4	**no**	0.52	147	88.6%	0.607
		yes	0.52	147	100%	0.678

† Calculated using expression (11)

‡Calculated using formula (12)