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Comparing adaptive interventions under a general sequential multiple assignment randomized trial design via multiple comparisons with the best

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ABSTRACT

This paper considers screening of adaptive interventions or adaptive treatment strategies embedded in a sequential multiple assignment randomized trial (SMART). As a SMART typically consists of numerous adaptive interventions, inferential procedures based on pairwise comparisons of all interventions may suffer substantial loss in efficiency after accounting for multiplicity. We propose simultaneous confidence intervals that compare the values of interventions of interest to that of the unknown best intervention by generalizing the method in Edwards and Hsu (1983). The multiple comparison with the best (MCB) intervals are applied as screening tool: an intervention with MCB interval excluding zero will be declared as inferior to the true best at a pre-specified confidence level, and hence excluded from further exploration. Simulation studies show that the proposed method outperforms the multiple comparison procedures based on Bonferroni's correction in terms of width of confidence intervals for estimation. The method is applied to analyze data from the CODIACS trial in patients with depression.

1. Introduction

An adaptive intervention (AI) is a sequence of treatment decisions made based on a patient's own historical clinical information, such as the treatment history and responses to the previous treatments, with the hope to improve or optimize treatment effect. A sequential multiple assignment randomized trial (SMART) consists of a collection of AIs randomly assigned to patients, providing information for the estimation of the optimal AIs (Murphy, 2005). The optimal AIs embedded in a SMART trial may be consistently selected by comparing the estimated values of all AIs, using procedures such as the G-computation under structural nested models (Robins, 1986; Lavori and Dawson, 2007) and the inverse probability weighted estimation under the marginal mean models (Murphy et al., 2001; Orellana et al., 2010). This approach entails multiple pairwise comparisons of AIs. As the number of AIs embedded in a SMART is often large, the pairwise comparison procedures, such as the Bonferroni's adjustment, are known to be conservative. To partially address this issue, gate-keeping approaches whereby pairwise comparisons of AIs will be made only after the hypothesis of no difference among the AIs of interest is rejected by an omnibus test have been proposed by Orellana et al. (2010), Nahum-Shani et al. (2012), Ogbagaber et al. (2016), Zhong et al. (2019).

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This article addresses the inferential problem of multiple comparison of AIs in a SMART by generalizing a simultaneous confidence intervals procedure proposed by Edwards and Hsu (1983). Specifically, we adopt the approach of multiple comparison with the best (MCB), a concept originated in the ranking and selection literature to address the subset selection problem (Hsu, 1981, 1984). The idea is to compare each treatment with the *unknown* best treatment, using a multiple comparison with the best confidence interval: treatments with multiple comparison with the best interval excluding zero (equivalently, upper limit less than zero) will be declared inferior and excluded from further investigation; while a treatment whose interval has 0 as its upper limit will be declared the best. The concept of multiple comparison with the best is appealing for a SMART where a typical goal is to identify one or several promising or near-best AIs and eliminate the inferior ones. The proposed method generalizes Edwards and Hsu (1983) in several respects. First, Edwards and Hsu (1983) considered non-adaptive interventions under parallel group designs where the correlation matrix among the intervention effects is known, while in our cases the interventions are adaptive under SMART and the correlation matrix among the AIs is both unknown and less than full rank (i.e., degenerate). Second, Edwards and Hsu (1983) required that the outcomes to be normally distributed with equal variance, while in this paper the outcomes are only required to be from an exponential family distribution.

Under the multiple testing framework, Ertefaie et al. (2016) proposed a method to construct a confidence set for the best adaptive intervention embedded in a sequential multiple assignment trial, a first attempt to address multiple comparisons of AIs via confidence set. However, there are some limitations of their work. First, they fail to realize that the asymptotic covariance of the AIs is not of full rank, which will cause loss of efficiency when ignored. Second, their proposed confidence set, which is an intermediate step of both our method and the original method proposed by Hsu (1984), yields a high false positive rate. Third, their method, which does not produce simultaneous confidence intervals, can not screen out inferior AIs as our method can do.

The rest of this article is organized as follows. Section 2 sets up notations, introduces an asymptotic distribution of the AIs, and proposes the method of building the MCB confidence intervals for comparing multiple AIs. The proposed simultaneous confidence intervals are evaluated using simulation in Section 3, and illustrated using a depression trial data set. This article ends with a discussion in Section 4. Technical detail is relegated to Appendix.

2. Method

For simplicity, we consider SMART designs with two-stage AIs. Suppose that there are I treatment options $T_1, \ldots, T_I$ at Stage 1, and under treatment T_i, there are J_i possible intermediate responses, denoted by $R_{i1}, \ldots, R_{iJ_i}$ for $i = 1, \ldots, I$. Next suppose that for a subject who receives treatment T_i at Stage 1 and has an intermediate response of R_{ij}, there are K_{ij} treatment options, namely $S_{ij1}, \ldots, S_{ijK_{ij}}$, at Stage 2. An AI can be written in the form of $d_{i;k_{i1},\ldots,k_{iJ_i}} = (T_i; S_{i1k_{i1}}, \ldots, S_{iJ_ik_{iJ_i}})$, where $(k_{i1}, \ldots, k_{iJ_i})$ is an element of the product set $\prod_{j=1}^{J_i}\{1, \ldots, K_{ij}\}$. Under this AI, a subject receives treatment T_i at Stage 1, and will receive treatment $S_{ijk_{ij}}$ at Stage 2 if an intermediate response of R_{ij} is observed, where $j = 1, \ldots, J_i$, $i = 1, \ldots, I$.

Let U_l denote the Stage-1 treatment received by subject l, X_l the intermediate response at the end of Stage 1 such that $\text{pr}(X_l = R_{ij}|U_l = T_i) = p_{ij}$. Let V_l be the Stage-2 treatment, and Y_l the primary outcome of interest for $l = 1, \ldots, n$. Let $\pi_i = \text{pr}(U_l = T_i)$ be the randomization probability of assigning T_i to subject l at Stage 1, and $\pi_{ijk} = \text{pr}(V_l = S_{ijk}|U_l = T_i, X_l = R_{ij})$ be the randomization probability of assigning treatment S_{ijk} to patient l given history of Stage-1 treatment and response $(U_l = T_i, X_l = R_{ij})$. The randomization scheme of a two-stage SMART is thus completely specified by the set of randomization probabilities $\{\pi_i, \pi_{ijk}\colon\ i = 1, \ldots, I;\ j = 1, \ldots, J_i;\ k = 1, \ldots, K_{ij}\}$. The data obtained from the lth subject who has completed a SMART can be summarized as (U_l, X_l, V_l, Y_l) for $l = 1, \ldots, n$, where $Y_l|(U_l = T_i, X_l = R_{ij}, V_l = S_{ijk})$ is assumed to have a probability density function $f\left(y_l|\phi_{ijk}, \tau_{ijk}\right)$, ϕ_{ijk} is the parameter of interest, and τ_{ijk}, possibly a vector, is a nuisance parameter.

Let

$$p_i = (p_{i1}, \ldots, p_{iJ_i})^T, \quad \phi_{ij} = (\phi_{ij1}, \ldots, \phi_{ijK_{ij}})^T, \quad \phi_i = (\phi_{i1}^T, \ldots, \phi_{iJ_i}^T)^T.$$

The value $\theta_{i;k_{i1},\ldots,k_{iJ_i}}$ of an AI $d_{i;k_{i1},\ldots,k_{iJ_i}}$ is defined as the marginal expected outcome Y under $d_{i;k_{i1},\ldots,k_{iJ_i}}$, and can be expressed as $\theta_{i;k_{i1},\ldots,k_{iJ_i}} = \sum_{j=1}^{J_i} p_{ij}\phi_{ijk_{ij}}$. Let θ_i be the vector of $\theta_{i;k_{i1},\ldots,k_{iJ_i}}$'s, arranged in the lexicographical order in $(k_{i1}, \ldots, k_{iJ_i})$. Then,

$$\theta_i = A_i\Lambda_i(p_i)\phi_i = A_i\Gamma_i(\phi_i)p_i, \tag{1}$$

where

$$A_i = (I_{K_{i1}} \otimes 1_{K_{i2}} \otimes \cdots \otimes 1_{K_{iJ_i}}|1_{K_{i1}} \otimes I_{K_{i2}} \otimes \cdots \otimes 1_{K_{iJ_i}}|\cdots|1_{K_{i1}} \otimes \cdots \otimes 1_{K_{i(J_i-1)}} \otimes I_{K_{iJ_i}}),$$

is a $G_i \times m_i$ matrix with $\otimes$ denoting the Kronecker product with $G_i = \prod_{j=1}^{J_i} K_{ij}$ and $m_i = \sum_{j=1}^{J_i} K_{ij}$, I_k is the $k \times k$ identity matrix, 1_k the $k \times 1$ matrix of 1's, and $\Lambda_i(p_i) = \text{bdiag}\{p_{ij}I_{K_{ij}};\ j = 1, \ldots, J_i\}$ is an $m_i \times m_i$ block diagonal matrix and $\Gamma_i(\phi_i) = \text{bdiag}\{\phi_{ij};\ j = 1, \ldots, J_i\}$ is an $m_i \times J_i$ block diagonal matrix with "bdiag{·}" denoting a block diagonal matrix.

As an illustration of Eq. (1), consider a SMART design with $I = 2, J_1 = J_2 = 2, K_{ij} \equiv 2$ and consider $i = 1$. Then,

$$\theta_1 = \begin{pmatrix} p_{11}\phi_{111} + p_{12}\phi_{121} \\ p_{11}\phi_{111} + p_{12}\phi_{122} \\ p_{11}\phi_{112} + p_{12}\phi_{121} \\ p_{11}\phi_{112} + p_{12}\phi_{122} \end{pmatrix} = \begin{pmatrix} 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{pmatrix} \begin{pmatrix} p_{11} & 0 & 0 & 0 \\ 0 & p_{11} & 0 & 0 \\ 0 & 0 & p_{12} & 0 \\ 0 & 0 & 0 & p_{12} \end{pmatrix} \begin{pmatrix} \phi_{111} \\ \phi_{112} \\ \phi_{121} \\ \phi_{122} \end{pmatrix}$$
$$= A_1 \Lambda_1(p_1)\phi_1,$$

where

$$A_1 = \begin{pmatrix} 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{pmatrix}$$

is as given by the formula on the previous page.

Now define $\Sigma_{p_i} = \pi_i^{-1}\left(\text{diag}\{p_i\} - p_i p_i^T\right)$, $\Sigma_{\phi_i} = \text{bdiag}\{\Sigma_{\phi_{i1}}, \ldots, \Sigma_{\phi_{ij_i}}\}$,

$$\Sigma_{\phi_{ij}} = \left(\pi_i p_{ij} \pi_{ijk}\right)^{-1} \text{bdiag}\left\{\sigma^2(\phi_{ijk}, \tau_{ijk});\ k = 1, \ldots, K_{ij}\right\},$$

and $\sigma^2(\phi_{ijk}, \tau_{ijk}) = \left(\imath_{\phi_{ijk}\phi_{ijk}} - \imath^T_{\phi_{ijk}\tau_{ijk}} \cdot \imath^{-1}_{\tau_{ijk}\tau_{ijk}} \cdot \imath_{\phi_{ijk}\tau_{ijk}}\right)^{-1}$, where

$$\begin{pmatrix} \imath_{\phi_{ijk}\phi_{ijk}} & \imath^T_{\phi_{ijk}\tau_{ijk}} \\ \imath_{\phi_{ijk}\tau_{ijk}} & \imath_{\tau_{ijk}\tau_{ijk}} \end{pmatrix}$$

is the block Fisher information matrix of distribution $f(y|\phi_{ijk}, \tau_{ijk})$.

Zhong et al. (2019) establish the following asymptotic distribution for the AIs.

Theorem 2.1. *Let $\theta = (\theta_1^T, \ldots, \theta_I^T)^T$. Assume the following regularity conditions:*

(C1) The true value θ is an interior point of Θ, the collection of all feasible parameters.

(C2) The second derivatives of $f(y_l|\phi_{ijk}, \tau_{ijk})$ are continuous as function of θ, and for any fixed interior point θ_0, there is a $\delta > 0$ such that

$$\sup_{\|\theta - \theta_0\| \le \delta} \|\nabla^2 f(y_l|\phi_{ijk}, \tau_{ijk})\| \le h_{\theta_0}(y_l), \qquad \int h_{\theta_0}(y_l) dy_l < \infty,$$

and

$$\sup_{\|\theta - \theta_0\| \le \delta} \|\nabla^2 \log f(y_l|\phi_{ijk}, \tau_{ijk})\| \le H_{\theta_0}(y_l), \quad E\left\{H_{\theta_0}(Y_l)\right\} < \infty,$$

where ∇ denotes the gradient operator with respect to θ.

Then, as $n \to \infty$,

$$\sqrt{n}(\hat{\theta} - \theta) \xrightarrow{d} N(0,\ \Sigma), \tag{2}$$

where $\Sigma = \text{bdiag}\{\Sigma_{\theta_1}, \ldots, \Sigma_{\theta_I}\}$, $\Sigma_{\theta_i} = A_i\left\{\Gamma_i(\phi_i)\Sigma_{p_i}\Gamma_i(\phi_i)^T + \Lambda_i(p_i)\Sigma_\phi\Lambda_i(p_i)\right\}A_i^T$, and $\text{rank}\left(\Sigma_{\theta_i}\right) = \sum_{j=1}^{J_i} K_{ij} - J_i + 1 = m_i - J_i + 1$, $i = 1, \ldots, I$.

We make three remarks. First, it can be easily verified that when $f(y_l|\phi_{ijk}, \tau_{ijk})$ forms an exponential family, the regularity conditions (C1) and (C2) in Theorem 2.1 are satisfied. Second, the asymptotic covariance matrix Σ_{θ_i} is obtained via the delta method and the fact that the asymptotic covariance matrix of $\hat{\phi}_i$, which is the MLE of ϕ_i, is the inverse of the Fisher information matrix. Third, it is interesting to note that the covariance matrix Σ is not of full rank. It is because the AIs are linearly dependent. To see this, consider a SMART with two Stage-1 treatment options, binary intermediate response, and three Stage-2 treatment options given any intermediate response. The total number of treatment sequences is 12 but the number of AIs is 18. Therefore, the values of AIs embedded in this SMART are linearly dependent, and their estimates are asymptotically linearly dependent, which means the asymptotic covariance matrix would have less than full rank.

We now describe a method to construct simultaneous confidence intervals for comparing AIs by extending the MCB idea in Edwards and Hsu (1983). For each $g = 1, \ldots, G$, let D_g be a $(G-1) \times G$ contrast matrix such that its gth column is a $(G-1)$ vector of 1's, and its jth column is a $(G-1)$-vector whose jth entry is -1 and other entries are 0's if $j \le g - 1$; whose $(j-1)$-th entry is -1 and other entries are 0's if $j \ge g + 1$. Then as $n \to \infty$,

$$D_g\ \sqrt{n}(\hat{\theta} - \theta) \xrightarrow{d} N\left(0,\ D_g \Sigma D_g^T\right).$$

Let σ_{ig}^2 be the ith diagonal entry of $D_g \Sigma D_g^T$. Then, the asymptotic variance can be expressed in terms of the correlation coefficient matrix R_g:

$$D_g \Sigma D_g^T = \text{diag}\{\sigma_{ig}\} \cdot R_g \cdot \text{diag}\{\sigma_{ig}\}.$$

For a given α, define $\delta_g(\alpha) > 0$ be the unique solution to the following equation

$$\text{pr}\left\{|Z_{ig}| \leq \delta_g(\alpha);\ i = 1, \ldots, G-1\right\} = \text{pr}\left\{\max_{i \in \{1,\ldots,G-1\}} |Z_{ig}| \leq \delta_g(\alpha)\right\} = 1 - \alpha,$$

where $\left(Z_{1g}, \ldots, Z_{G-1,g}\right)^T \sim N(0,\ \hat{R}_g)$ and $\hat{R}_g$ is a consistent estimator of R_g.

To obtain $\hat{R}_g$, observe that R_g is a continuous function of $p_i, \phi_i, \Sigma_{p_i}, \Sigma_{\phi_i}$, $i = 1, \ldots, I$. We know from Theorem 2.1 that the MLEs of $\hat{p}_i, \hat{\phi}_i, \hat{\Sigma}_{p_i}, \hat{\Sigma}_{\phi_i}$ are consistent. By the continuous mapping theorem, the plug-in estimator $\hat{R}_g$ will be consistent of R_g. Furthermore, from Theorem 2.1, we know that Σ and hence R_g is not of full rank. In fact, from the rank of Σ we conclude that the $G - \sum_{i=1}^{I} m_i + \sum_{i=1}^{I} J_i - I$ smallest eigenvalues of R_g must be 0. To improve efficiency of $\hat{R}_g$, the $G - \sum_{i=1}^{I} m_i + \sum_{i=1}^{I} J_i - I$ smallest eigenvalues of $\hat{R}_g$ are forced to be 0 to match those of R_g. Specifically, consider eigendecomposition $\hat{R}_g = \hat{V}\hat{E}\hat{V}^T$, where $\hat{E}$ is the diagonal matrix of eigenvalues of $\hat{R}_g$ and $\hat{V}$ an orthogonal matrix of eigenvalues. Let $\tilde{E}$ be the diagonal matrix by replacing the $G - \sum_{i=1}^{I} m_i + \sum_{i=1}^{I} J_i - I$ smallest eigenvalues of $\hat{E}$ by 0's. Then, $\tilde{R}_g = \hat{V}\tilde{E}\hat{V}^T$ is an improved estimator of R_g upon the original $\hat{R}_g$.

We remove α from $\delta_g(\alpha)$ in the subsequent text for brevity. Let

$$\mathcal{G} = \left\{g : \hat{\theta}_g - \hat{\theta}_i + \delta_g \hat{\sigma}_{ig}/\sqrt{n} > 0,\ \text{for all } i \neq g\right\},$$

where n is the total sample size of the study and $\hat{\sigma}_{ig}$ is the plug-in estimator of σ_{ig}, the standard deviation of the ith diagonal entry of $D_g \Sigma D_g^T$. The MCB interval $[L_i, U_i]$ for the ith AI is calculated as

$$L_i = \min_{g \in \mathcal{G}} L_{ig} \text{ and } U_i = \max_{g \in \mathcal{G}} U_{ig},$$

where

$$L_{ig} = \begin{cases} 0, & \text{if } g = i, \\ \hat{\theta}_i - \hat{\theta}_g - \delta_g \hat{\sigma}_{ig}/\sqrt{n}, & \text{if } g \neq i, \end{cases} \quad \text{and} \quad U_{ig} = \begin{cases} 0, & \text{if } g = i, \\ \min\left\{0, \hat{\theta}_i - \hat{\theta}_g + \delta_g \hat{\sigma}_{ig}/\sqrt{n}\right\}, & \text{if } g \neq i. \end{cases}$$

Theorem 2.2. *As $n \to \infty$, the intervals $[L_i, U_i]$, $i = 1, \ldots, G$, constructed above is a set of $100(1-\alpha)\%$ asymptotic simultaneous confidence intervals for $\theta_i - \max_{j \in \{1,\ldots,G\}} \theta_j$, $i = 1, \ldots, G$. Furthermore, when there is a unique g^* such that $\theta_{g^*} > \theta_i, i \neq g^*$, the asymptotic coverage of the above simultaneous confidence interval is exactly $1 - \alpha$; otherwise, the asymptotic coverage is $> 1 - \alpha$.*

Theorem 2.2, whose proof is given in the Appendix, implies that the proposed intervals $[L_i, U_i]$ are for comparison with the truly best $\max_j \theta_j$ *without* assuming the knowledge of which AI is the true best. By construction, no upper limit U_i can be positive, that is, $U_i \leq 0$ for all i. An AI whose corresponding upper limit U_i is negative is considered inferior to optimal with confidence. Furthermore, if the set $\mathcal{G} = \{g^*\}$ is a singleton, the MCB interval associated with that AI must be $[0, 0]$, that is, $L_{g^*} = 0$. Conversely, it can be shown that if $L_{g'} = 0$ for some g', then the set $\mathcal{G} = \{g'\}$ is a singleton.

3. Numerical studies

3.1. Simulation

Three two-stage SMART designs are considered in the simulation (Fig. 1). The first design structure (DS1) mimics the situation in CODIACS (cf. Table 1, which pertains to the data to be analyzed in Section 3.2) and many other situations where there are two treatment options at each decision making point, that is, $T_i, S_{ijk} \in \{0, 1\}$, and binary intermediate response, that is, $R_{ij} \in \{0, 1\}$ for $i, j, k = 1, 2$. As a result, there are eight possible AIs embedded in DS1. Under DS2 and DS3, there are also two treatment options at Stage 1. However, randomization at Stage 2 may be restricted for patients with certain intermediate responses, resulting in 4 and 3 embedded AIs in DS2 and DS3, respectively.

Under each design structure, a SMART design is completely specified by the set $\{\pi_i, \pi_{ijk}\}$ of randomization probabilities defined in Section 2. In the simulation, we considered three sets of randomization probabilities. First, we considered balanced randomization (BR), that is, $\text{pr}(U = 1) = 0.5$ and $\text{pr}(V = 1|U, X) = 0.5$ whenever there is an option of randomization at Stage 2. Second, we considered an unbalanced randomization (UBR) scheme, where $\text{pr}(U = 1) = 0.7$ and $\text{pr}(V = 1|U, X) = 0.7$ whenever there is an option of Stage-2 randomization. Third, we considered $\text{pr}(U = 1) = 0.5$ at Stage 1, $\text{pr}(V = U|U, X = 0) = 0.3$ and $\text{pr}(V = U|U, X = 1) = 0.7$, whenever there is an option of second stage randomization. Under this scheme, Stage 2 implements an adaptive randomization (AR) rule for the situations where the first and the second stage treatment options are identical. In summary, the three design structures (DS1, DS2, DS3) and the

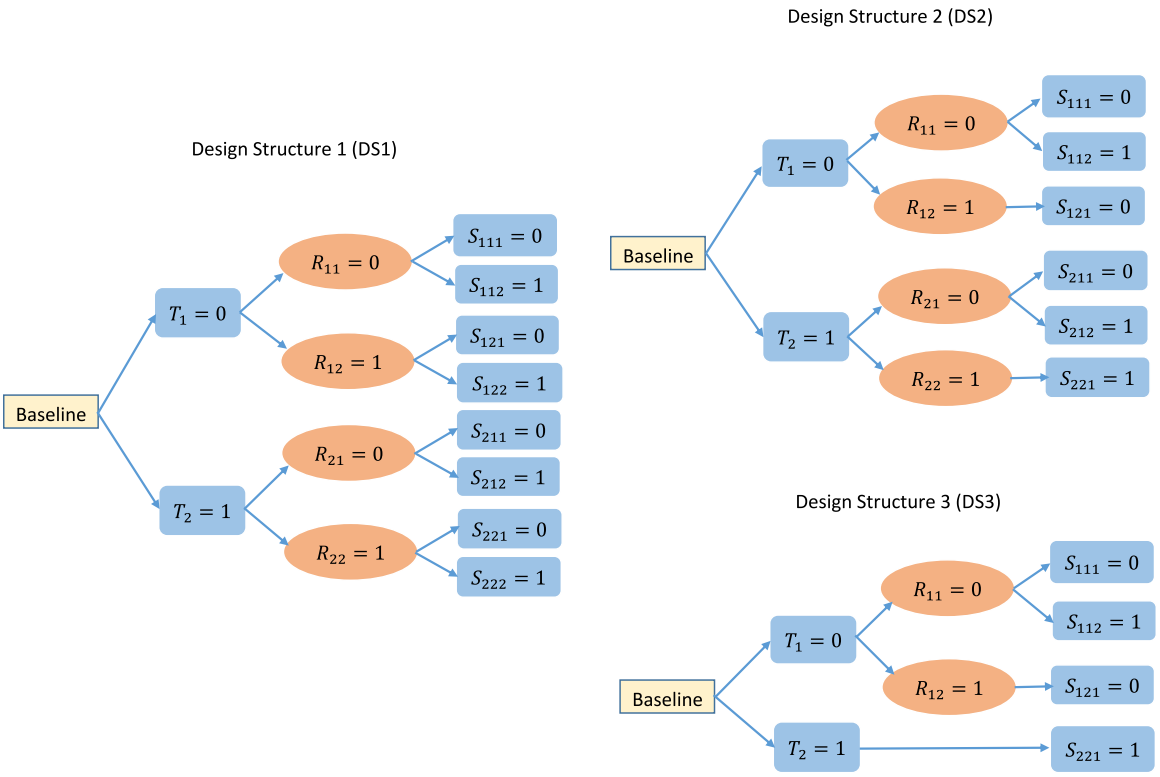

Fig. 1. Design structures in the simulations.

Table 1
Multiple comparison of adaptive interventions embedded in CODIACS study. The MCB intervals for AI g compares it with the true (unknown) best AI, whereas the Bonferroni's intervals compare with the observed best. sd: asymptotic standard deviation of $\hat{\theta}_g$ (from inverse of Fisher information matrix); Med: Medication; PST: Problem-solving therapy.

AI (g)	Stage-1	Stage-2 Treatment for		$\hat{\theta}_g$ (sd)	δ_g	80% confidence intervals	
	Treatment	non-response	response			MCB	Bonferroni
1	Med	Med	Med	6.3 (1.1)	1.98	[−19.7, 0.0]	[−25.7, 7.3]
2	Med	Med	PST	3.3 (1.2)	1.99	[−22.7, −0.3]	[−28.7, 4.5]
3	Med	PST	Med	10.7 (0.6)	2.04	[−15.2, 0.0]	[−21.1, 11.8]
4	Med	PST	PST	7.8 (1.1)	1.98	[−18.2, 0.0]	[−24.2, 8.8]
5	PST	Med	Med	15.45 (6.0)	1.71	[−7.6, 0.0]	–
6	PST	Med	PST	9.5 (1.0)	2.00	[−16.3, 0.0]	[−22.2, 10.2]
7	PST	PST	Med	14.2 (6.1)	1.71	[−8.9, 0.0]	[−3.8, 1.4]
8	PST	PST	PST	8.2 (1.1)	1.98	[−17.6, 0.0]	[−23.6, 9.1]

three randomization schemes (BR, UBR, AR) yielded 9 SMART designs under which the multiple comparison procedures were evaluated.

Under each SMART design with n subjects, the treatment assignment (U_l, V_l) of the lth patient was generated according to one of the three randomization schemes. The intermediate response rate was set as $\text{pr}(X_l = 1|U_l = T_i) = 1/3$ for $T_i \in \{0, 1\}$. Given the lth subject's treatment history and intermediate response (T_i, R_{ij}, S_{ijk}), his or her outcome Y_l was randomly generated from a normal distribution with mean $\phi_{ijk} = \phi(T_i, R_{ij}, S_{ijk})$ and variance $\sigma^2 = 100$, where the conditional mean ϕ_{ijk} was specified as

$$\phi(T_i, R_{ij}, S_{ijk}) = \beta_0 + \beta_1 T_i + \beta_2 R_{ij} + \beta_3 S_{ijk} + \beta_4 T_i R_{ij} + \beta_5 T_i S_{ijk} + \beta_6 R_{ij} S_{ijk} + \beta_7 T_i R_{ij} S_{ijk}$$

for $T_i, R_{ij}, S_{ijk} \in \{0, 1\}$. The parameter $\beta = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7)^T$ was chosen so that the true AI values $\theta_{i;k_{i1},\ldots,k_{ij}}$'s would follow the patterns displayed in Fig. 2. Under Value Pattern 1 (VP1), AIs with the same Stage-1 treatment had the same values; under VP2, the values of the AIs were uniformly higher if their Stage-1 treatment was $U = 1$; under VP3, the best AI had Stage-1 treatment $U = 1$ while the second best had Stage-1 treatment $U = 0$, and so on and so forth, following an alternating pattern. The value of β was chosen so that the effect size Δ, which measures the heterogeneity among the AIs, was either 0.05 or 0.10. The β's used in the simulation scenarios are given in Table 2.

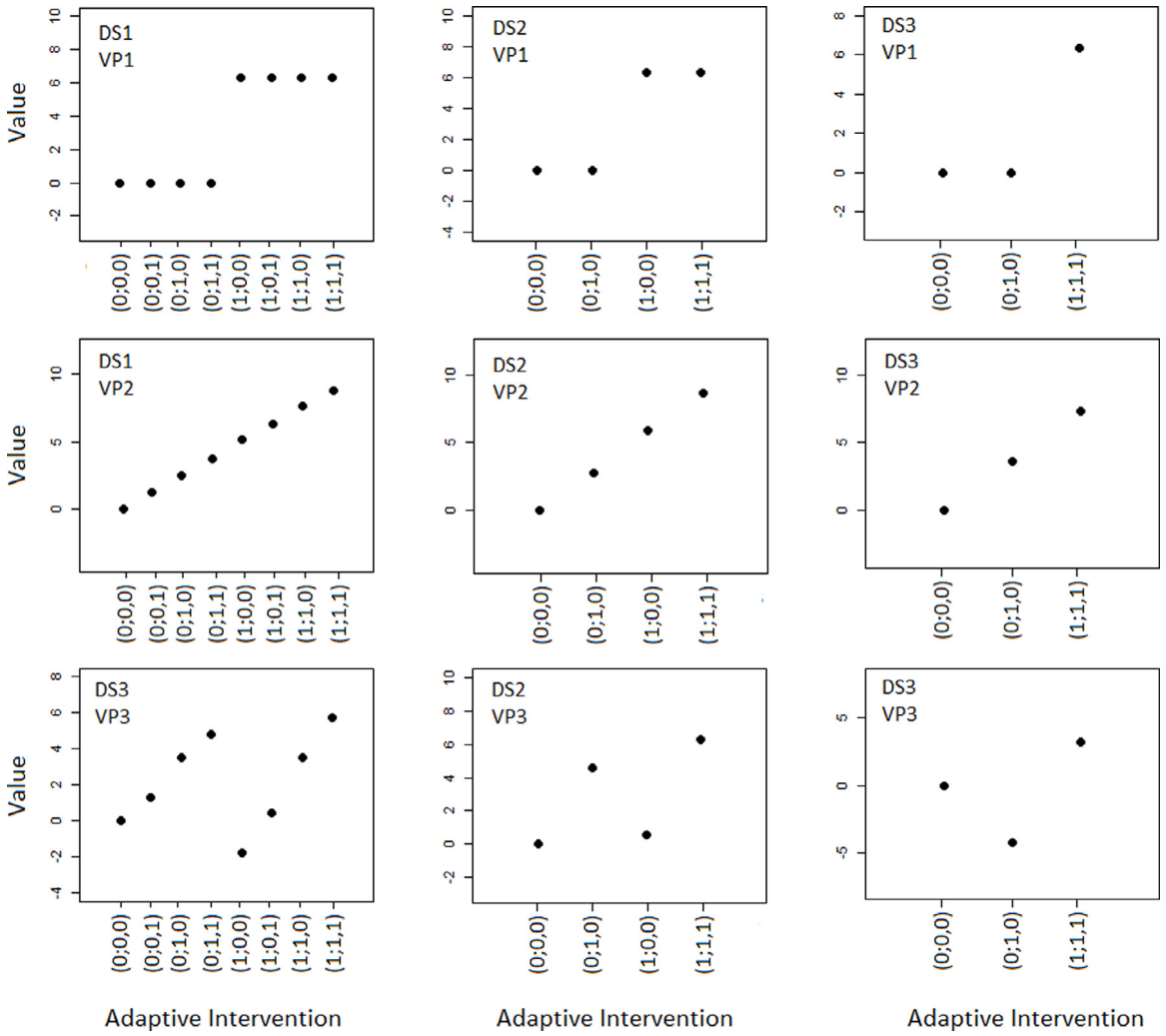

Fig. 2. Value patterns of AIs in the simulations.

Table 2
Values of $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7)$ used in the simulations.

Scenario	$(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7)$	
	$\Delta = 0.05$	$\Delta = 0.10$
DS1-VP1	(0.00, 4.48, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)	(0.00, 6.33, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)
DS1-VP2	(0.00, 3.63, 0.00, 2.62, 0.00, 0.00, 0.00, 0.00)	(0.00, 5.13, 0.00, 3.70, 0.00, 0.00, 0.00, 0.00)
DS1-VP3	(0.00, 1.86, 0.00, 3.73, −9.32, 1.86, −0.93, 0.00)	(0.00, 2.64, 0.00, 5.82, −13.20, 2.64, −1.32, 0.00)
DS2-VP1	(0.00, 4.48, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)	(0.00, 6.33, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)
DS2-VP2	(0.00, 0.00, 0.00, 2.88, 12.00, 0.00, 0.00, 0.00)	(0.00, 0.00, 0.00, 4.13, 17.70, 0.00, 0.00, 0.00)
DS2-VP3	(0.00, −1.21, 0.00, 4.82, 4.82, 1.21, 0.00, 0.00)	(0.00, −1.72, 0.00, 6.87, 6.87, 1.72, 0.00, 0.00)
DS3-VP1	(0.00, 4.48, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)	(0.00, 6.33, 0.00, 0.00, 0.00, 0.00, 0.00, 0.00)
DS3-VP2	(0.00, 1.29, 0.00, 3.88, 0.00, 0.00, 0.00, 0.00)	(0.00, 1.82, 0.00, 5.47, 0.00, 0.00, 0.00, 0.00)
DS3-VP3	(0.00, 0.00, 0.00, −4.46, 0.00, 6.69, 0.00, 0.00)	(0.00, 0.00, 0.00, −6.36, 0.00, 9.54, 0.00, 0.00)

Our multiple comparison procedure applies the MCB confidence intervals for the purpose of treatment screening: AIs with MCB intervals excluding zero will be declared inferior to the optimal AI and removed from further considerations. To anticipate the clinical context where there are many candidate treatments (AIs) and the goal is to move forward with a subset, we may consider applying the MCB intervals at a confidence level less than 95% so as to afford a higher differentiating power. Specifically, we consider 80% confidence in this subsection.

Table 3
Properties of 80% MCB intervals and simultaneous confidence intervals using Bonferroni's adjustment with $n = 200$: coverage probability (cov) and average width of intervals (wid).

Scenario	$\Delta = 0.05$				$\Delta = 0.10$			
	MCB		Bonferroni		MCB		Bonferroni	
	cov	wid	cov	wid	cov	wid	cov	wid
DS1-VP1-BR	0.927	6.63	0.918	5.42	0.920	6.95	0.918	5.42
DS1-VP1-UBR	0.941	7.07	0.927	6.31	0.925	7.47	0.927	6.31
DS1-VP1-AR	0.929	7.13	0.920	5.72	0.921	7.52	0.920	5.72
DS1-VP2-BR	0.901	6.64	0.915	8.63	0.867	7.10	0.915	8.65
DS1-VP2-UBR	0.913	7.24	0.924	9.52	0.873	7.73	0.921	9.53
DS1-VP2-AR	0.907	7.13	0.917	9.57	0.876	7.67	0.916	9.59
DS1-VP3-BR	0.936	6.64	0.905	8.81	0.903	7.30	0.903	8.99
DS1-VP3-UBR	0.960	7.70	0.919	9.63	0.946	8.37	0.915	9.75
DS1-VP3-AR	0.942	7.10	0.904	9.74	0.914	7.77	0.901	9.90
DS2-VP1-BR	0.881	4.95	0.866	3.90	0.880	5.09	0.866	3.90
DS2-VP1-UBR	0.885	5.36	0.864	4.80	0.870	5.54	0.864	4.80
DS2-VP1-AR	0.883	5.28	0.858	3.82	0.877	5.44	0.858	3.82
DS2-VP2-BR	0.858	5.00	0.889	5.75	0.848	5.19	0.893	5.88
DS2-VP2-UBR	0.865	5.30	0.878	6.02	0.846	5.48	0.879	6.11
DS2-VP2-AR	0.838	5.37	0.877	6.47	0.835	5.65	0.882	6.60
DS2-VP3-BR	0.872	4.97	0.873	5.67	0.857	5.23	0.876	5.72
DS2-VP3-UBR	0.886	5.35	0.876	5.98	0.867	5.67	0.880	6.03
DS2-VP3-AR	0.856	5.30	0.869	6.41	0.840	5.61	0.872	6.45
DS3-VP1-BR	0.806	3.52	0.843	4.00	0.805	3.47	0.841	4.00
DS3-VP1-UBR	0.813	4.31	0.852	4.79	0.808	4.23	0.852	4.79
DS3-VP1-AR	0.807	3.70	0.843	4.17	0.805	3.64	0.843	4.17
DS3-VP2-BR	0.821	3.66	0.846	4.01	0.815	3.62	0.846	4.02
DS3-VP2-UBR	0.839	4.55	0.854	4.80	0.828	4.58	0.854	4.82
DS3-VP2-AR	0.821	3.75	0.848	4.19	0.818	3.74	0.850	4.20
DS3-VP3-BR	0.809	3.67	0.841	4.02	0.798	3.66	0.840	4.03
DS3-VP3-UBR	0.815	4.33	0.845	4.81	0.801	4.39	0.844	4.83
DS3-VP3-AR	0.821	3.94	0.833	4.19	0.800	3.93	0.829	4.21

Table 3 gives the coverage probabilities of the 80% MCB intervals under various designs and outcome scenarios based on 5000 simulation runs, which will yield an estimated standard error of accuracy to the second decimals. In addition, we point out our estimators, being MLEs, are asymptotically efficient, which implies that their standard errors should be smallest asymptotically. To be more concise, each probability pertained to simultaneous coverage, and was calculated as the proportion of simulated trials under which the gth MCB interval covers the corresponding true values of $\theta_g - \max_{i\in\{1,\ldots,G\}} \theta_i$ for *all* $g = 1, \ldots, G$. Recall that $G = 8, 4, 3$ under DS1, DS2, and DS3, respectively. For comparison purposes, we also considered simultaneous confidence intervals based on Bonferroni's correction: For each pair of AIs, a confidence interval for the difference of their values was evaluated with confidence level $100\,[1 - 0.2/\{G(G-1)/2\}]\%$ so that the overall nominal coverage is 80%. The coverage probability of the Bonferroni intervals was calculated as the proportion of simulated trials under which all $G(G-1)/2$ intervals covered the corresponding true differences. While we note that the Bonferroni's simultaneous confidence intervals address a different estimation problem than the MCB intervals, both methods are valid in that their corresponding coverage probabilities were at least 80% in all scenarios. Indeed, both methods appeared to be conservative, especially under DS1 where there were many AIs. For MCB intervals, the conservativeness was due to the asymptotic approximation: simulation with larger sample size showed that the coverage probability approaches the nominal 80% as n increased.

We also calculated the average widths of the confidence intervals as a measure of efficiency. For the MCB method, the average width was taken over the G MCB intervals. For the Bonferroni's pairwise intervals, the average width was taken over the G intervals that compared to the *observed* best AI. We note that this comparison was unfair against MCB intervals in two ways due to the interpretation of the intervals. First, the MCB intervals did not assume the knowledge of the *true* best AI, and the calculation of MCB intervals implicitly accounted for variability induced due to this unknown parameter. In contrast, the Bonferroni's method avoided estimating the unknown true best AI by comparing all AIs against a known and observed best, and thus was addressing an easier inferential problem. Second, by definition of the Bonferroni pairwise intervals, the observed best when compared to itself would have a width of zero, which would artificially shrink the average width towards a smaller value. However, we opted to use the Bonferroni's intervals as a benchmark to evaluate how the MCB intervals perform under different scenarios. Having noted the difference in interpretation of the two interval estimation procedures and the average widths, we observe that the 80% MCB intervals had smaller average width than the average of the G corresponding Bonferroni's intervals under value patterns VP2 and VP3, but had larger average width under VP1. And the MCB intervals were narrower than the Bonferroni ones under the third design structure irrespective of the value pattern. As discussed above, since the MCB intervals implicitly account for the variability in estimating what the true best AI is, we expect larger variability when the true best AI is not unique and thus difficult to estimate,

Table 4
The probability of an AI being declared inferior using 80% MCB intervals under balanced randomization (BR) and a sample size $n = 200$.

AI	$\Delta = 0.05$						$\Delta = 0.10$					
	DS1-VP1		DS1-VP2		DS1-VP3		DS1-P1		DS1-VP2		DS1-VP3	
	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.
(0;0,0)	0.00	0.382	0.00	0.461	0.00	0.197	0.00	0.781	0.00	0.857	0.00	0.460
(0;0,1)	0.00	0.391	0.87	0.324	0.93	0.098	0.00	0.785	1.23	0.709	1.32	0.236
(0;1,0)	0.00	0.379	1.74	0.227	2.49	0.038	0.00	0.778	2.47	0.533	3.52	0.080
(0;1,1)	0.00	0.381	2.62	0.156	3.42	0.025	0.00	0.785	3.70	0.361	4.84	0.046
(1;0,0)	4.48	0.014	3.63	0.122	−1.24	0.343	6.33	0.015	5.13	0.299	−1.76	0.726
(1;0,1)	4.48	0.013	4.50	0.050	0.31	0.115	6.33	0.015	6.36	0.111	0.44	0.334
(1;1,0)	4.48	0.015	5.38	0.015	2.49	0.034	6.33	0.017	7.60	0.046	3.52	0.074
(1;1,1)	4.48	0.017	6.25	0.001	4.04	0.005	6.33	0.019	8.83	0.000	5.72	0.005
AI	DS2-VP1		DS2-VP2		DS2-VP3		DS2-VP1		DS2-VP2		DS2-VP3	
	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.
(0;0,1)	0.00	0.667	0.00	0.734	0.00	0.549	0.00	0.943	0.00	0.976	0.00	0.885
(0;1,1)	0.00	0.663	1.92	0.440	3.21	0.119	0.00	0.945	2.77	0.759	4.58	0.191
(1;0,1)	4.48	0.033	4.00	0.234	0.40	0.442	6.33	0.034	5.90	0.462	0.57	0.773
(1;1,1)	4.48	0.041	5.92	0.001	4.42	0.008	6.33	0.041	8.67	0.000	6.30	0.003
AI	DS3-VP1		DS3-VP2		DS3-VP3		DS3-VP1		DS3-VP2		DS3-VP3	
	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.	Value	Prob.
(0;0,1)	0.00	0.830	0.00	0.820	0.00	0.401	0.00	0.987	0.00	0.983	0.00	0.630
(0;1,1)	0.00	0.835	2.59	0.492	−2.97	0.830	0.00	0.987	3.65	0.748	−4.24	0.982
(1;1,1)	4.48	0.000	5.17	0.000	2.23	0.001	6.33	0.000	7.30	0.000	3.18	0.000

i.e., under VP1. In practice, scenarios such as VP1 where many AIs have the same value are conceivably less likely than the other patterns, especially when the AIs consist of components of different treatment types (i.e., pharmacological vs. behavioral).

Table 4 presents the probability of an AI being declared inferior using 80% MCB intervals under balanced randomization (BR) with $n = 200$, based on 5000 simulation runs. As Δ increased from 0.05 to 0.10, the truly inferior AIs were correctly identified with increasing probabilities. Specifically, under $\Delta = 0.10$ with $n = 200$, the MCB method identified the true worst AI as inferior with probabilities between 73% and 98%. Similar results were obtained for the other two types of randomization (data not shown).

3.2. Example of the CODIACS trial for depression

Cheung et al. (2015) analyzed data in a subset of patients enrolled to the CODIACS trial with an objective to further determine which stepped care depression management regimens should be used and which should be discontinued in an implementation stage. A specific task may thus be formulated as eliminating inferior AIs from further practice based on reduction of Beck Depression Inventory at 6 months, which was the primary endpoint in the original study. In other words, the value of an intervention in this application is the expected reduction of the depression score. Furthermore, each AI would adapt to an initial response at 8 weeks defined as no increase in depression. Table 1 shows the 80% MCB intervals for the eight possible two-stage AIs embedded in the study. This analysis identified an inferior AI, namely, the AI with $g = 2$ that would start with medication, stay with it upon a non-response, and switch to problem-solving therapy upon a response. We emphasize that this analysis was not intended to estimate the true best AI with statistical confidence. Rather, the utility of this analysis is to exclude the inferior AI from further practice from a quality assurance viewpoint.

As a comparison, we applied the pairwise confidence intervals with Bonferroni's correction described above. Table 1 also lists the intervals that compare each AI with the *observed* best, and shows that the Bonferroni's correction failed to differentiate any AIs. From an estimation viewpoint, the MCB intervals give more precise estimates than Bonferroni's: the average widths of the 8 MCB intervals were shorter than that of the 7 Bonferroni's intervals. Note that there was no Bonferroni interval for $g = 5$. This is because for the Bonferroni method, we treated, although unreasonably, the observed optimal AI $g = 5$ (for $\hat{\theta}_5$ is the largest) as the *true* optimal and the confidence intervals were constructed for the remaining 7 AIs by comparing them against $g = 5$. So, $g = 5$, being considered as the true optimal AI, had itself no confidence interval associated with it.

4. Discussion

In many situations, it is appropriate to view a SMART as a study in a series of experimental studies that lead to a confirmatory trial (Murphy, 2005). In the early phase where there are potentially many treatment options, a relevant clinical objective would be to eliminate inferior AIs (or non-adaptive interventions) so that the clinical investigation can quickly zero in on the promising interventions. The concept of screening has been well-studied in the contexts of clinical

trials and multiple comparison in experimental designs (Bechhofer et al., 1995). A contribution of this article is to extend the screening concept to the evaluation of adaptive interventions, thus enhancing the practicality of SMARTs.

The proposed method generalizes Edwards and Hsu (1983) in several respects. First, Edwards and Hsu (1983) considered non-adaptive interventions under parallel group designs where the correlation among the intervention effects are known, while in our cases the interventions are adaptive under SMART and the correlation among the adaptive interventions are both unknown and less than full rank (i.e., degenerate). Second, Edwards and Hsu (1983) required that the outcomes to be normally distributed with equal variance, while in this paper the outcomes are only required to be from an exponential family distribution. In fact, as long as the joint asymptotic distribution of the AIs can be obtained (Cf. Theorem 2.1), the proposed method will remain valid. These are certainly topics for further study. Having said that, we note that the results in this article are derived under weak assumptions on the (conditional) distribution of the outcome Y, with the exponential family being the most prominent example that the theory is applicable to. Thus, the specific procedures studied in this article shall have applications in very broad settings.

Finally, when there are multiple optimal AIs, the simultaneous confidence interval provided in Theorem 2.2 is shown to be conservative. Further research is needed to improve the performance in these situations.

CRediT authorship contribution statement

Xiaobo Zhong: Methodology, Writing - original draft. **Ying Kuen Cheung:** Methodology, Data curation, Writing - original draft. **Min Qian:** Methodology, Writing - review & editing. **Bin Cheng:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

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Appendix

Proof of Theorem 2.2. Let $g^* = \text{argmax}_{i\in\{1,\ldots,G\}}\theta_i$, where ties can be broken in any fashion without affecting the validity of the proof. Consider

$$E = \left\{\hat{\theta}_i - \theta_i - \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n} \le \hat{\theta}_{g^*} - \theta_{g^*} \le \hat{\theta}_i - \theta_i + \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n};\ i \ne g^*\right\}.$$

By the construction of δ_{g^*},

$$\lim_{n\to\infty} \text{pr}(E) = 1 - \alpha.$$

Since

$$\hat{\theta}_{g^*} - \theta_{g^*} \ge \hat{\theta}_i - \theta_i - \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n}$$

for all $i \ne g^*$ is equivalent to

$$\hat{\theta}_{g^*} - \hat{\theta}_i + \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n} \ge \theta_{g^*} - \theta_i \ge 0$$

for all $i \ne g^*$, we conclude that $g^* \in \mathcal{G}$.

From

$$\hat{\theta}_{g^*} - \theta_{g^*} \le \hat{\theta}_i - \theta_i + \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n},$$

we have

$$\theta_i - \theta_{g^*} \le \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n},$$

and noticing that $\theta_i - \theta_{g^*} \le 0$, we conclude that

$$\begin{aligned} E &\subseteq \left\{g^* \in \mathcal{G}, \theta_i - \theta_{g^*} \le \min\left(0, \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n}\right), i \ne g^*\right\} \\ &\subseteq \left\{\theta_i - \theta_{g^*} \le U_i, i = 1, \ldots, G\right\}. \end{aligned}$$

Similarly,

$$\begin{aligned} E &\subseteq \left\{g^* \in \mathcal{G}, \theta_i - \theta_{g^*} \ge \hat{\theta}_i - \hat{\theta}_{g^*} - \delta_{g^*}\hat{\sigma}_{ig^*}/\sqrt{n}, i \ne g^*\right\} \\ &\subseteq \left\{\theta_i - \theta_{g^*} \ge L_i, i = 1, \ldots, G\right\}. \end{aligned}$$

Thus,

$$E \subseteq \left\{ L_i \le \theta_i - \theta_{g^*} \le U_i, i = 1, \ldots, G \right\},$$

and

$$\begin{aligned} &\mathrm{pr}\left(L_i \le \theta_i - \max_{j \in \{1,\ldots,G\}} \theta_j \le U_i, i = 1, \ldots, G \right) \\ &= \mathrm{pr}\left(L_i \le \theta_i - \theta_{g^*} \le U_i, i = 1, \ldots, G \right) \ge \mathrm{pr}(E). \end{aligned}$$

Therefore,

$$\liminf_{n\to\infty} \mathrm{pr}\left(L_i \le \theta_i - \max_{j \in \{1,\ldots,G\}} \theta_j \le U_i, i = 1, \ldots, G \right) \ge \lim_{n\to\infty} \mathrm{pr}(E) = 1 - \alpha.$$

Now we proceed to prove the claims on asymptotic coverage. First, consider the case when there exists a single g^* such that $\theta_{g^*} > \theta_i, i \ne g^*$. That is, when the optimal AI is unique. In this case, recalling the construction of the simultaneous confidence intervals and the consistency of $\hat{\theta}_j$'s, we conclude that, when n large enough, the simultaneous confidence interval for $\theta_i - \theta_{g^*}$, $i \ne g^*$, becomes

$$[L_i, U_i] = \begin{cases} \{0\} & \text{if } i = g^*, \\ \left[\hat{\theta}_i - \hat{\theta}_{g^*} - \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n}, \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right] & \text{if } i \ne g^*. \end{cases}$$

Thus, the asymptotic coverage is

$$\begin{aligned} &\lim_{n\to\infty} \mathrm{pr}\left(\theta_i - \theta_{g^*} \in \left[\hat{\theta}_i - \hat{\theta}_{g^*} - \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n}, \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right], \text{for all } i \ne g^* \right) \\ &= \mathrm{pr}\left\{ |Z_{ig^*}| \le \delta_{g^*};\ i \ne g^* \right\} = \mathrm{pr}\left\{ \max_{i \ne g^*} |Z_{ig^*}| \le \delta_{g^*} \right\} = 1 - \alpha, \end{aligned}$$

by the definition of δ_{g^*}.

Now consider the case when the optimal AI is *not* unique. Without loss of generality, assume that there exists a $k \le G - 2$ such that $\max\{\theta_1, \ldots, \theta_k\} < \theta_{k+1} = \cdots = \theta_G$. That is, there are $G - k \ge 2$ optimal AIs. By the construction of the simultaneous confidence intervals, we conclude that, when n large enough, the confidence interval for $\theta_i - \max_j\{\theta_j\}$ is $\{0\}$ if $i \in \{k+1, \ldots, G\}$; and when $i \in \{1, \ldots, k\}$, $[L_i, U_i]$, the confidence interval for $\theta_i - \max_j\{\theta_j\}$, becomes

$$\left[\min_{g^* \in \{k+1,\ldots,G\}} \left\{ \hat{\theta}_i - \hat{\theta}_{g^*} - \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right\}, \max_{g^* \in \{k+1,\ldots,G\}} \left\{ \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right\} \right].$$

The asymptotic coverage is

$$\begin{aligned} &\liminf_{n\to\infty} \mathrm{pr}\left(\min_{g^* \in \{k+1,\ldots,G\}} \left\{ \hat{\theta}_i - \hat{\theta}_{g^*} - \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right\} \le \theta_i - \theta_{g^*} \right. \\ &\left. \le \max_{g^* \in \{k+1,\ldots,G\}} \left\{ \hat{\theta}_i - \hat{\theta}_{g^*} + \delta_{g^*} \hat{\sigma}_{ig^*}/\sqrt{n} \right\}, i = 1, \ldots, k \right) \\ &\ge \liminf_{n\to\infty} \mathrm{pr}\left(\hat{\theta}_i - \hat{\theta}_G - \delta_G \hat{\sigma}_{iG}/\sqrt{n} \le \theta_i - \theta_G \le \hat{\theta}_i - \hat{\theta}_G + \delta_G \hat{\sigma}_{iG}/\sqrt{n}, i = 1, \ldots, k \right) \\ &= \mathrm{pr}\left(\max_{i \in \{1,\ldots,k\}} |Z_{iG}| \le \delta_G \right) > \mathrm{pr}\left(\max_{i \in \{1,\ldots,G-1\}} |Z_{iG}| \le \delta_G \right) = 1 - \alpha, \end{aligned}$$

as claimed. □

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