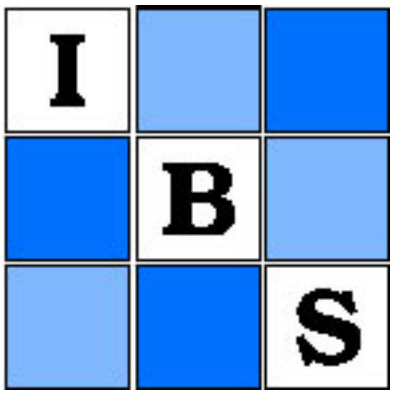

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A Computationally Simpler Algorithm for the UMVUE of a Normal Mean Following a Group Sequential Trial

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SUMMARY

When using data collected in a group sequential clinical trial, the sample mean is no longer the uniform minimum variance unbiased estimator (UMVUE) of the mean of a normal distribution. Emerson (1993, *Computers and Biomedical Research*, **26,** 68–73) described an algorithm for computing the UMVUE in this setting. This algorithm, although computationally expensive, used only the basic software necessary for deriving group sequential boundaries. In this paper, we present an improved algorithm that results in greatly decreased computation times.

1. Introduction

It is now commonplace for clinical trials to be conducted using a group sequential stopping rule to monitor for patient safety. There have been many methods proposed in the statistical literature for the design (e.g., Wang and Tsiatis, 1987; Emerson and Fleming, 1989; Whitehead, 1992), monitoring (Lan and DeMets, 1983; Pampallona, Tsiatis, and Kim, 1995), and analysis (Tsiatis, Rosner, and Mehta, 1984; Whitehead, 1986; Emerson and Fleming, 1990) of such group sequential trials. In general, the implementation of those methods is computer intensive, and specialized programs are necessary to make full use of the advantages afforded by group sequential testing. In commercial programs, the introduction of techniques for estimation following a group sequential trial has lagged the introduction of techniques for the design and monitoring of a trial. The reasons for this delay are several, including the more recent focus on estimation methodology, the lack of widespread agreement on the most appropriate methods, and the computational complexity of some methods. In this communication, we are concerned with the computational complexity of one otherwise attractive group sequential estimator. For a more detailed discussion of the role of specialized estimation techniques for group sequential trials and a comparative review of two commercially available software packages for group sequential methods, see Emerson (1996).

In the group sequential setting, there are more criteria that can be used to compare point estimators than there are in the nonsequential, fixed-sample situation. Emerson and Fleming (1990) compared a number of point estimators that adjust for the group sequential stopping rule used to collect the data. In that comparison, no single estimator was found to satisfy all criteria. The uniform minimum variance unbiased estimator (UMVUE) had the advantage of unbiasedness, acceptable mean squared error, and dependence only on the group sequential stopping boundaries at times up to and including the analysis at which the trial was terminated. The chief disadvantage of the UMVUE was its computational complexity. Emerson (1993) described an algorithm for

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determination of the UMVUE that was computationally tractable. However, even with the use of this algorithm, the time required to calculate the UMVUE for a trial stopped at the third of four analyses was typically several times longer than the combined time required to calculate all other point estimates, interval estimates, and P values. We describe here a modification of that algorithm that results in computational speeds for the UMVUE that are generally faster than those for the other adjusted point estimators.

2. Group Sequential Tests

The data consist of the potential random observations $X_i, i = 1, \ldots, N_K$, where the X_i's are independent and identically distributed according to $\mathcal{N}(\mu, \sigma^2)$, with the variance σ^2 assumed to be known. Analyses of the data are conducted when $N_1, N_2, \ldots, N_K$ subjects have been accrued, where K is the maximum number of analyses to be performed. For notational convenience, we define $n_1 = N_1$ and, for $k = 2, \ldots, K$, $n_k = N_k - N_{k-1}$ as the size of the groups accrued between successive analyses. We consider the problem of estimating the unknown parameter μ, which is asymptotically applicable to a wide variety of situations (Whitehead, 1992).

In this estimation problem, we are affected by the group sequential design only through its impact on the sampling density for our data. We are unconcerned with issues related to the type I and II statistical errors arising from the interpretation placed on specific results. Hence, for our purposes, the group sequential stopping rule is defined by specifying for each analysis the results that will cause the trial to continue, and we need not address the decision to be made when the trial stops. That is, for each $k = 1, \ldots, K$, the statistic $S_k = \Sigma_{i=1}^{N_k} X_i$ is compared to a continuation set $\mathcal{C}_k \subset (-\infty, \infty)$. The first time S_k is not in the continuation set $\mathcal{C}_k$, we stop the study. The choice of the empty set for the continuation set at the Kth analysis, $\mathcal{C}_K = \emptyset$, guarantees that the trial terminates at or before that analysis.

The sufficient statistic for the unknown normal mean μ can be shown to be (M, S), where M is the number of the analysis at which the study terminated and $S = S_M$ (Chang, 1989). The density for the test statistic (M, S) can be computed after the method of Armitage, McPherson, and Rowe (1969) as

$$p(m, s; \mu) = \begin{cases} f(m, s; \mu) & \text{if } s \notin \mathcal{C}_m \\ 0 & \text{otherwise,} \end{cases} \tag{1}$$

with $f(m, s; \mu)$ recursively defined by

$$f(1, s; \mu) = \frac{1}{\sqrt{n_1}\sigma} \phi\left(\frac{s - n_1\mu}{\sqrt{n_1}\sigma}\right), \tag{2}$$

$$f(m, s; \mu) = \int_{\mathcal{C}_{m-1}} \frac{1}{\sqrt{n_m}\sigma} \phi\left(\frac{s - u - n_m\mu}{\sqrt{n_m}\sigma}\right) f(m-1, u; \mu)\, du \quad (m = 2, \ldots, K), \tag{3}$$

where $\phi(x)$ is the standard normal density. A computationally useful form of this density is

$$f(m, s; \mu) = f(m, s; 0) \exp\left(\frac{s\mu}{\sigma^2} - \frac{\mu^2}{2\sigma^2} N_m\right). \tag{4}$$

It is generally impossible to compute the integrals involved in the density in closed form, and thus determining the stopping boundaries for a group sequential test typically involves extensive numerical integration on a computer. Furthermore, due to the recursive nature of the density, the computation of $p(m, s; \mu)$ involves calculating $f(k, u; \mu)$ for a grid of values of $u \in \mathcal{C}_k$ for $1 \leq k < m$.

In the above density, it is also useful to note that the density for observation $(M = m, S = s)$ depends on neither the sample sizes nor the continuation sets of analyses after the mth. That is, the function $f(m, s; \mu)$ is independent of $N_{m+1}, \ldots, N_K$ and $\mathcal{C}_{m+1}, \ldots, \mathcal{C}_K$.

3. Formula for the UMVUE

Consider a group sequential study having a stopping boundary defined by continuation sets $\mathcal{C}_1, \ldots, \mathcal{C}_K$ for analyses conducted when the accrued sample sizes are $N_1, \ldots, N_K$, respectively. Suppose the trial is terminated with observation $(M = m, S = s)$. Using the Rao–Blackwell improvement theorem (Lehmann, 1983), the estimator based on the expected value of the unbiased statistic S_1/N_1 conditioned on the sufficient statistic (N_M, S) will have lower variance than S_1/N_1. The argument presented in Emerson (1993) that this estimator is the UMVUE is incorrect, because it is not clear that (N_M, S) is complete. However, in recent unpublished research at the

University of Rochester, Aiyu Liu and W. J. Hall have shown that the estimator constructed using Rao–Blackwell is the UMVUE among all estimators that do not require knowledge of the number and timing of future analyses (W. J. Hall, personal communication).

Emerson (1993) described an algorithm for the computation of the UMVUE using only software necessary for calculation of the density of (M, S). In that algorithm, the UMVUE $\hat{\mu}$ is computed as

$$\begin{aligned}\hat{\mu} &= \mathrm{E}\left[\frac{S_1}{n_1} \mid (M,S) = (m,s)\right] \\ &= \int_{\mathcal{C}_1} \frac{s_1}{n_1} p_{S_1|(M,S)}(s_1 \mid (M,S) = (m,s))\, ds_1 \\ &= \frac{\int_{\mathcal{C}_1} \frac{s_1}{n_1} p^{(s_1)}(m-1, s-s_1; \mu)\, p(1, s_1; \mu)\, ds_1}{p(m,s;\mu)},\end{aligned} \tag{5}$$

where the density $p(\cdot,\cdot;\mu)$ is defined using (1)–(3) with the $\mathcal{C}_k$'s and N_k's, and the density $p^{(s_1)}(\cdot,\cdot;\mu)$ is calculated for each value of s_1 using (1)–(3) for a 'shifted' group sequential test having sample sizes and continuation sets for $k = 1, \ldots, m-1$ given by

$$\begin{aligned}\mathcal{C}_k^{(s_1)} &= \mathcal{C}_{k+1} - s_1 = \{x : x + s_1 \in \mathcal{C}_{k+1}\} \\ n_k^{(s_1)} &= n_{k+1}.\end{aligned}$$

In the above formulation, the 'shifted' group sequential test depends on the integration variable s_1. Thus, when numerically integrating (5), a new density $p^{(s_1)}$ must be calculated for each new value of s_1. The computational cost of this approach is due to the recursive numerical integrations needed to evaluate (3) to obtain specific values of $p^{(s_1)}$.

Improvements in this algorithm can be achieved by the following result. Let $p(\cdot,\cdot;\mu)$ be the density according to (1)–(3) for the group sequential test defined by sample sizes $N_1, \ldots, N_K$ and continuation sets $\mathcal{C}_1, \ldots, \mathcal{C}_K = \emptyset$, and let $p^*(\cdot,\cdot;\mu)$ be the density according to (1)–(3) for another group sequential test defined for some $2 \le \ell \le K$ by sample sizes $N_1^*, \ldots, N_\ell^*$, group sizes $n_1^* = N_1^*$ and $n_k^* = N_k^* - N_{k-1}^*$ for $k = 2, \ldots, \ell$, and continuation sets $\mathcal{C}_1^*, \ldots, \mathcal{C}_\ell^* = \emptyset$. Suppose that the group sizes and continuation sets for the two group sequential tests are related according to

$$\begin{aligned}&n_k^* = n_{\ell+1-k}, \quad k = 1, \ldots, \ell \\ &\mathcal{C}_k^* = u_\ell - \mathcal{C}_{\ell-k} = \{x : u_\ell - x \in \mathcal{C}_{\ell-k}\}, \quad k = 1, \ldots, \ell-1\end{aligned}$$

for some $u_\ell \notin \mathcal{C}_\ell$. Then

$$p(\ell, u_\ell; \mu) = p^*(\ell, u_\ell; \mu). \tag{6}$$

This equivalence is shown for the case $\mu = 0$ by expanding the recursive relationship in (3) to obtain

$$\begin{aligned}&p(\ell, u_\ell; 0) \\ &= \int_{\mathcal{C}_{\ell-1}} \cdots \int_{\mathcal{C}_1} \frac{1}{\sqrt{n_\ell}\sigma}\phi\left(\frac{u_\ell - u_{\ell-1}}{\sqrt{n_\ell}\sigma}\right) \cdots \frac{1}{\sqrt{n_2}\sigma}\phi\left(\frac{u_2 - u_1}{\sqrt{n_2}\sigma}\right) \frac{1}{\sqrt{n_1}\sigma}\phi\left(\frac{u_1}{\sqrt{n_1}\sigma}\right) du_1 \cdots du_{\ell-1} \\ &= \int_{\mathcal{C}_{\ell-1}^*} \cdots \int_{\mathcal{C}_1^*} \frac{1}{\sqrt{n_\ell^*}\sigma}\phi\left(\frac{u_\ell - v_{\ell-1}}{\sqrt{n_\ell^*}\sigma}\right) \cdots \frac{1}{\sqrt{n_2^*}\sigma}\phi\left(\frac{v_2 - v_1}{\sqrt{n_2^*}\sigma}\right) \frac{1}{\sqrt{n_1^*}\sigma}\phi\left(\frac{v_1}{\sqrt{n_1^*}\sigma}\right) dv_1 \cdots dv_{\ell-1} \\ &= p^*(\ell, u_\ell; 0),\end{aligned}$$

where the second equation follows from the first by changing the variables of integration according to $v_k = u_\ell - u_{\ell-k}$ for $k = 1, \ldots, \ell-1$, and rearranging the order of integration. The generalization to the case of an arbitrary value of μ is straightforward.

We now apply the result in (6) to the problem of computing the density $p^{(s_1)}(m-1, s-s_1; \mu)$ for a 'shifted' group sequential test. Thus, for $\ell = m-1$ and $u_\ell = s - s_1$, we use the correspondences

$$\begin{aligned}&n_k^* = n_{m-k}^{(s_1)} = n_{m-k+1}, \quad k = 1, \ldots, m-1 \\ &\mathcal{C}_k^* = s - s_1 - \mathcal{C}_{m-1-k}^{(s_1)} = s - \mathcal{C}_{m-k}, \quad k = 1, \ldots, m-2.\end{aligned} \tag{7}$$

We then obtain

$$\hat{\mu} = \frac{\int_{\mathcal{C}_1} \frac{s_1}{n_1} p^*(m-1, s-s_1; \mu)\, p(1, s_1; \mu)\, ds_1}{p(m, s; \mu)}, \tag{8}$$

where the density $p(\cdot, \cdot; \mu)$ is defined using (1)–(3) with the $\mathcal{C}_k$'s and N_k's, and the density $p^*(\cdot, \cdot; \mu)$ is calculated for each value of s_1 using (1)–(3) for a group sequential test having sample sizes and continuation sets given by (7). For instance, if the continuation sets for a group sequential test are given by

$$\mathcal{C}_k = (a_k, b_k) \cup (c_k, d_k),$$

then the density $p^*(\cdot, \cdot; \mu)$ is computed using continuation sets

$$\mathcal{C}_k^* = (s - d_{m-k}, s - c_{m-k}) \cup (s - b_{m-k}, s - a_{m-k}).$$

At an intuitive level, the original algorithm calculated the joint density of a given S_1 and (M, S) by considering all sample paths starting at $(1, S_1)$ and ending at (M, S). In the revised algorithm, we essentially reverse those sample paths to start at (M, S) and end at $(1, S_1)$. In each algorithm, the continuation sets are defined based on the start of the sample path. The revised algorithm allows a single set of boundaries to be used for all values of S_1, rather than requiring the computation of new boundaries (and hence new sequential densities) for each value of S_1 used in the numerical integration.

We note that, owing to the sufficiency of (M, S), the computed UMVUE is the same regardless of the value of μ used in its computation. Some convenience is gained through the choice of $\mu = 0$, in which case the symmetry of the standard normal density can be used to derive a slightly different formulation for the UMVUE. Let $p(\cdot, \cdot; 0)$ be the density for a group sequential test based on sample sizes and continuation sets denoted by N_k and $\mathcal{C}_k$ for $k = 1, \ldots, m$, and let $p^-(\cdot, \cdot; 0)$ be the density for a group sequential test based on the same sample sizes denoted by N_k but continuation sets denoted by $\mathcal{C}_k^-$ for $k = 1, \ldots, m$. If

$$\mathcal{C}_k^- = -\mathcal{C}_k = \{x : -x \in \mathcal{C}_k\},$$

then $p(m, s; 0) = p^-(m, -s; 0)$. Hence, it is easily shown that we can use the correspondences

$$\begin{aligned} n_k^* &= n_{m-k+1}, \quad k = 1, \ldots, m-1 \\ \mathcal{C}_k^* &= \mathcal{C}_{m-k} - s, \quad k = 1, \ldots, m-2 \end{aligned} \tag{9}$$

to compute the density $p^*(\cdot, \cdot; 0)$, and then compute the UMVUE according to

$$\hat{\mu} = \frac{\int_{\mathcal{C}_1 - s} \frac{u+s}{n_1} p^*(m-1, u; 0)\, p(1, u+s; 0)\, du}{p(m, s; 0)}. \tag{10}$$

Because neither the sample sizes nor the continuation sets defined in (7) are dependent upon s_1, the same group sequential density is being used for every value of s_1 in the numerical integration. Thus, in contrast with the earlier algorithm (Emerson, 1993), the numerical integration to find the UMVUE involves only a single additional density. This translates into significant savings in computational time. When computing a UMVUE for a hypothetical trial stopped at the fourth analysis ($M = 4$), the conversion of a program to use the formulation for the UMVUE specified by (8) resulted in speeds over 100 times faster than those same programs achieved with the previous algorithm. Such performance greatly enhances the utility of the UMVUE in estimating treatment effects at the conclusion of a group sequential trial.

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Résumé

Lorsque l'on travaille sur les données d'un essai clinique séquentiel, l'estimateur non biaisé, et de variance uniformément minimale, de la moyenne d'une variable gaussienne (estimateur dont les initiales en anglais sont notées UMVUE) n'est plus la moyenne de l'échantillon. Emerson (1993, *Computers and Biomedical Research* **26,** 68–73) a du reste présenté un algorithme permettant de calculer l'estimateur UMVUE dans ce contexte, algorithme qui, quoique coûteux en temps de calcul,

n'utilisait que l'information minimale nécessaire à la détermination des valeurs-seuils liées aux tests séquentiels. Dans cet article, nous présentons un algorithme amélioré qui permet de diminuer les temps de calcul.

References

Armitage, P. K., McPherson, C. K., and Rowe, B. C. (1969). Repeated significance tests on accumulating data. *Journal of the Royal Statistical Society, Series A* **132,** 235–244.

Chang, M. N. (1989). Confidence intervals for a normal mean following a group sequential test. *Biometrics* **45,** 247–254.

Emerson, S. S. (1993). Computation of the uniform minimum variance unbiased estimator of a normal mean following a group sequential trial. *Computers and Biomedical Research* **26,** 68–73.

Emerson, S. S. (1996). Software packages for group sequential tests. *American Statistician* **50,** 183–192.

Emerson, S. S. and Fleming, T. R. (1989). Symmetric group sequential designs. *Biometrics* **45,** 905–923.

Emerson, S. S. and Fleming, T. R. (1990). Parameter estimation following group sequential hypothesis testing. *Biometrika* **77,** 875–892.

Lan, K. K. G. and DeMets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70,** 659–663.

Lehmann, E. L. (1983). *Theory of Point Estimation.* New York: Wiley.

Pampallona, S. A., Tsiatis, A. A., and Kim, K. M. (1995). *Spending functions for the type I and type II error probabilities of group sequential tests.* Technical Report, Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts.

Tsiatis, A. A., Rosner, G. L., and Mehta, C. R. (1984). Exact confidence intervals following a group sequential test. *Biometrics* **40,** 797–803.

Wang, S. K. and Tsiatis, A. A. (1987). Approximately optimal one-parameter boundaries for group sequential trials. *Biometrics* **43,** 193–199.

Whitehead, J. (1986). On the bias of maximum likelihood estimation following a sequential test. *Biometrika* **73,** 573–581.

Whitehead, J. (1992). *The Design and Analysis of Sequential Clinical Trials,* 2nd edition. Chichester: Ellis Horwood.

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