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Blinded Sample Size Re-estimation Using Nuisance Parameters in Clinical Trials

A theoretical note on blinded continuous monitoring for continuous outcomes

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This work is done under the supervision of Prof. Tim Friede.

Contents:

1 Introduction

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Assume $X_1, \dots, X_n \sim N(\mu_1, \sigma^2)$, $Y_1, \dots, Y_n \sim N(\mu_2, \sigma^2)$.
We aim to determine the optimal sample size for testing $\boldsymbol{H_0: \mu_1 = \mu_2}$ in a two-sample setting. The test should control the **type I error rate at level $\boldsymbol{\alpha}$**, and achieve **power $\boldsymbol{1-\beta}$** for detecting the prespecified treatment difference $\boldsymbol{\delta_a}$.

Fixed-sample design: we calculate the optimal sample size for each group

$$\boldsymbol{n_{req} = v\sigma^2}$$

where $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

1 Introduction

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$$\boldsymbol{n_{req} = v\sigma^2}$$

where $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

Remarks:
- **In practice, the true value σ^2 is unknown.**

Sequential procedure:

Motivated by the expression of n_{req} for known σ^2, Friede and Miller (2012) suggested the following sequential procedure.

Let

$$N = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}_n^2 \leq n/v\}$$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

- Notice that N will be stopped when the stopping rule $\hat{\sigma}_n^2 \leq n/v$ is met.
- We monitor the variance for each n until the stopping rule is met.

Friede, T., & Miller, F. (2012). Blinded continuous monitoring of nuisance parameters in clinical trials. *Journal of the Royal Statistical Society Series C: Applied Statistics*, 61(4), 601-618.

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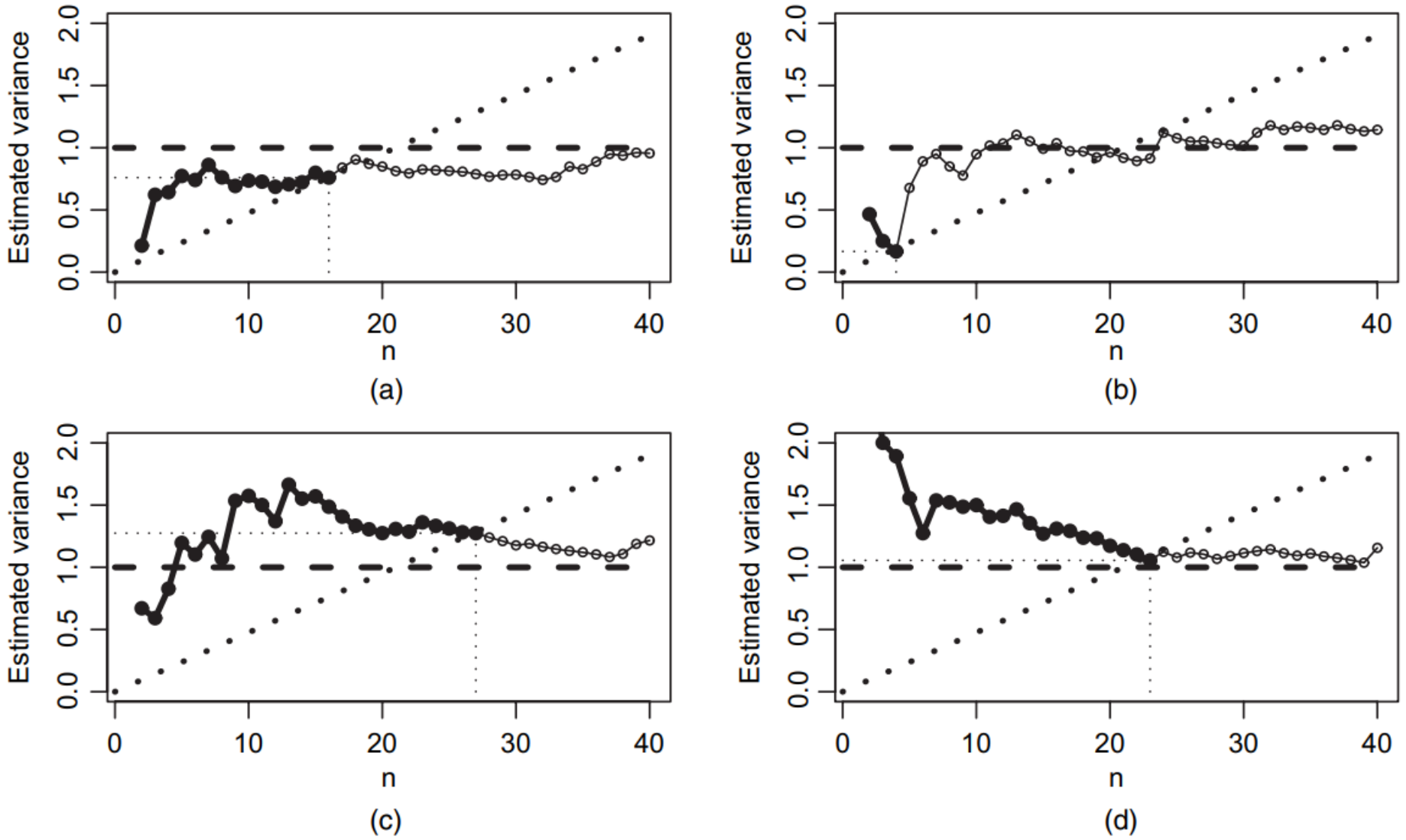

Fig. 1. Four simulated variance processes $(\hat{\sigma}_n^2)_n$ with stopping boundary n/v (⋰), $v = 21.0$: ●, trial until stop; ○, hypothetical continuation of the trial beyond the stop decision; – – –, true variance $\sigma^2 = 1$; ·····, ⋮, stopping time and variance estimate at termination

Friede and Miller (2012) *Journal of the Royal Statistical Society, Series C (Applied Statistics)*

Sequential procedure:

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where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

- **Potential advantages: Stopping trials early, Fewer patient recruited**

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How to choose variance estimator $\hat{\sigma}_n^2$?

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2 Unblinded and blinded variance estimator

Assume $X_1, \dots, X_n \sim N(\mu_1, \sigma^2)$, $Y_1, \dots, Y_n \sim N(\mu_2, \sigma^2)$.

For simplicity, we assume here that the observations in the study are made in blocks of two, i.e. we observe patients in pairs (X_i, Y_i), always one with treatment group and one with control group.

For convenience, denote $\boldsymbol{Z} = (Z_1, \dots, Z_{2n}) = (X_1, Y_1, \dots, X_n, Y_n)$ as blinded sample. Let $\bar{X} = (\sum_{i=1}^{n} X_i)/n$, $\bar{Y} = (\sum_{i=1}^{n} Y_i)/n$. Denote $\bar{Z} = \sum_{i=1}^{n}(X_i + Y_i)/(2n) = (\bar{X} + \bar{Y})/2$.

	with incorporating information about treatment assignment	**without incorporating information about treatment assignment**
	Unblind	**Blind**
Pair 1	(X_1, Y_1)	(Z_1, Z_2)
Pair 2	(X_2, Y_2)	(Z_3, Z_4)
Pair 3	(X_3, Y_3)	(Z_5, Z_6)
…	…	…
…	…	…
Pair n	(X_n, Y_n)	(Z_{2n-1}, Z_{2n})

X_i: from treatment group

Y_i: from control group

2 Unblinded and blinded variance estimator

Assume $X_1, \dots, X_n \sim N(\mu_1, \sigma^2)$, $Y_1, \dots, Y_n \sim N(\mu_2, \sigma^2)$.

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1. Unblind: **with incorporating information about treatment assignment**

$$\hat{\sigma}^2_{n,unblind} = \frac{1}{2n-2}\left(\sum_{i=1}^{n}(X_i - \bar{X})^2 + \sum_{j=1}^{n}(Y_j - \bar{Y})^2\right) = \frac{1}{2}\left(\frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2 + \frac{1}{n-1}\sum_{j=1}^{n}(Y_j - \bar{Y})^2\right)$$

2. Blind: **without incorporating information about treatment assignment**

$$\hat{\sigma}^2_{n,blind} = \frac{1}{2n-1}\sum_{i=1}^{2n}(Z_i - \bar{Z})^2$$

View these data as one-sample

$$= \frac{1}{2n-1}\left(\sum_{i=1}^{n}(X_i - \bar{Z})^2 + \sum_{j=1}^{n}(Y_j - \bar{Z})^2\right)$$

$$= \frac{1}{2n-1}\left(\sum_{i=1}^{n}(X_i - \bar{X})^2 + \sum_{j=1}^{n}(Y_j - \bar{Y})^2 + \frac{n(\bar{X} - \bar{Y})^2}{2}\right)$$

2 Unblinded and blinded variance estimator

Assume $X_1, \dots, X_n \sim N(\mu_1, \sigma^2)$, $Y_1, \dots, Y_n \sim N(\mu_2, \sigma^2)$.

For simplicity, we assume here that the observations in the study are made in blocks of two, i.e. we observe patients in pairs (X_i, Y_i), always one with treatment group and one with control group.

For convenience, denote $\boldsymbol{Z} = (Z_1, \dots, Z_{2n}) = (X_1, Y_1, \dots, X_n, Y_n)$ as blinded sample. Let $\bar{X} = (\sum_{i=1}^{n} X_i)/n$, $\bar{Y} = (\sum_{i=1}^{n} Y_i)/n$. Denote $\bar{Z} = \sum_{i=1}^{n}(X_i + Y_i)/(2n) = (\bar{X} + \bar{Y})/2$.

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2. Blind: **without incorporating information about treatment assignment**

$$\hat{\sigma}^2_{n,blind} = \frac{1}{2n-1}\sum_{i=1}^{2n}(Z_i - \bar{Z})^2$$

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• Comparison

Assume $X_1, ..., X_n \sim N(\mu_1, \sigma^2)$, $Y_1, ..., Y_n \sim N(\mu_2, \sigma^2)$. Let $\bar{X} = (\sum_{i=1}^n X_i)/n$, $\bar{Y} = (\sum_{i=1}^n Y_i)/n$. Denote $\bar{Z} = \sum_{i=1}^n (X_i + Y_i)/(2n) = (\bar{X} + Y)/2$.

1. Unblind: **with** incorporating information about treatment assignment

$$\hat{\sigma}^2_{n,unblind} = \frac{1}{2n-2}\left(\sum_{i=1}^n (X_i - \bar{X})^2 + \sum_{j=1}^n (Y_j - \bar{Y})^2\right) = \frac{1}{2}\left(\frac{1}{n-1}\sum_{i=1}^n (X_i - \bar{X})^2 + \frac{1}{n-1}\sum_{j=1}^n (Y_j - \bar{Y})^2\right)$$

$(2n-2)\hat{\sigma}^2_{n,unblind}/\sigma^2 \sim \chi^2_{2n-2}$ **Chi-squared distribution**

$\mathbb{E}(\hat{\sigma}^2_{n,unblind}) = \sigma^2$ **Unbiased estimator**

$\hat{\sigma}^2_{n,unblind} \overset{a.s.}{\to} \sigma^2 \quad as\ n \to \infty$ **Consistent estimator**

2. Blind: **without** incorporating information about treatment assignment

$$\begin{aligned}
\hat{\sigma}^2_{n,blind} &= \frac{1}{2n-1}\sum_{i=1}^{2n} (Z_i - \bar{Z})^2 \\
&= \frac{1}{2n-1}\left(\sum_{i=1}^n (X_i - \bar{Z})^2 + \sum_{j=1}^n (Y_j - \bar{Z})^2\right) \\
&= \frac{1}{2n-1}\left(\sum_{i=1}^n (X_i - \bar{X})^2 + \sum_{j=1}^n (Y_j - \bar{Y})^2 + \frac{n(\bar{X} - \bar{Y})^2}{2}\right)
\end{aligned}$$

$(2n-1)\hat{\sigma}^2_{n,blind}/\sigma^2 \sim \chi^2_{2n-1}(\lambda)$ where $\lambda = n(\mu_1 - \mu_2)^2/(2\sigma^2)$. **Noncentral chi-squared distribution**

$\mathbb{E}(\hat{\sigma}^2_{n,blind}) = \sigma^2 + \frac{n}{2(2n-1)}(\mu_1 - \mu_2)^2$ **Biased estimator**

$\hat{\sigma}^2_{n,blind} \overset{a.s.}{\to} \sigma^2 + (\mu_1 - \mu_2)^2/4 \quad as\ n \to \infty$

For more statistical properties, the readers can refer to Friede and Kieser (2013) *Pharmaceutical Statistics*

Background

$N = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}_n^2 \leq n/v\}$ where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$

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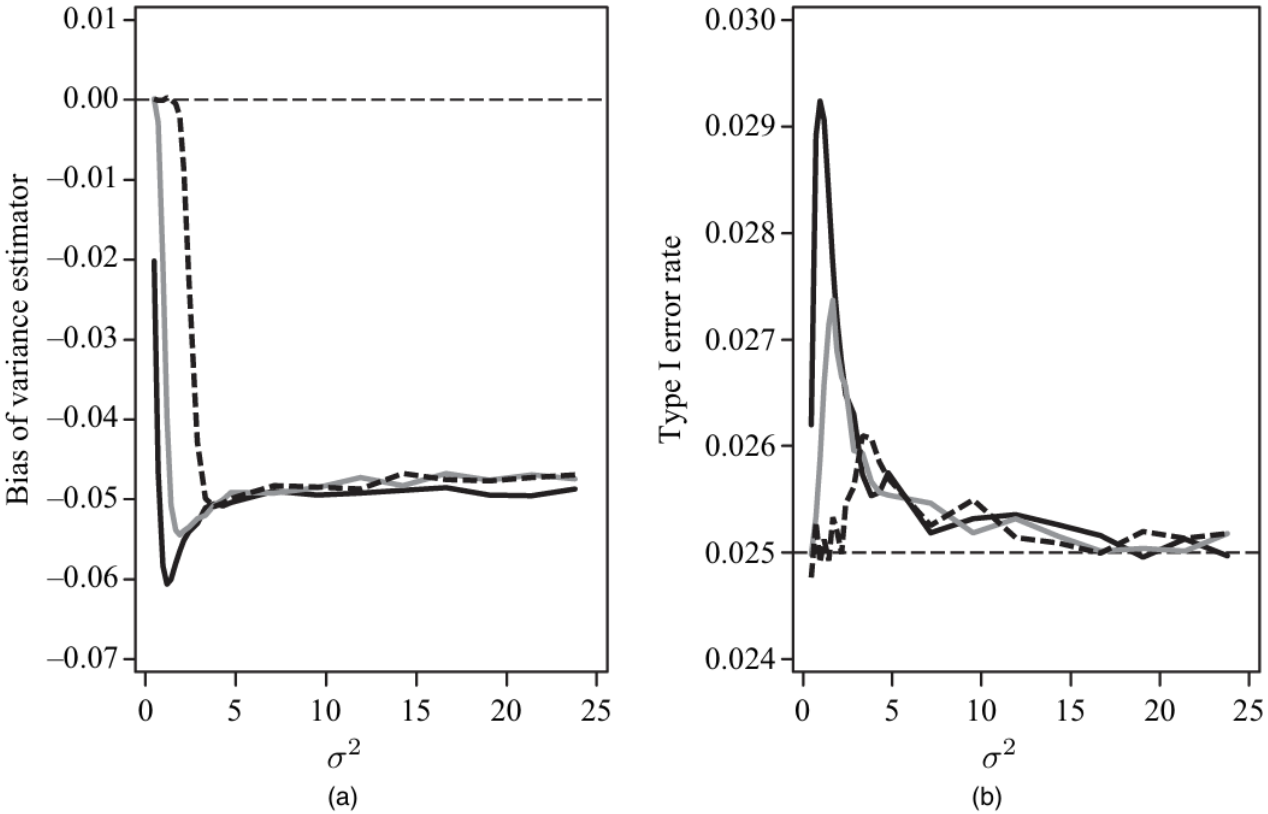

Fig. 2. (a) Bias of the variance estimator and (b) size of the *t*-test after unblinded continuous monitoring for $n_1 = 10$ (———), $n_1 = 20$ (———) and $n_1 = 50$ (– – –) depending on the true variance σ^2 for nominal $\alpha = 0.025$

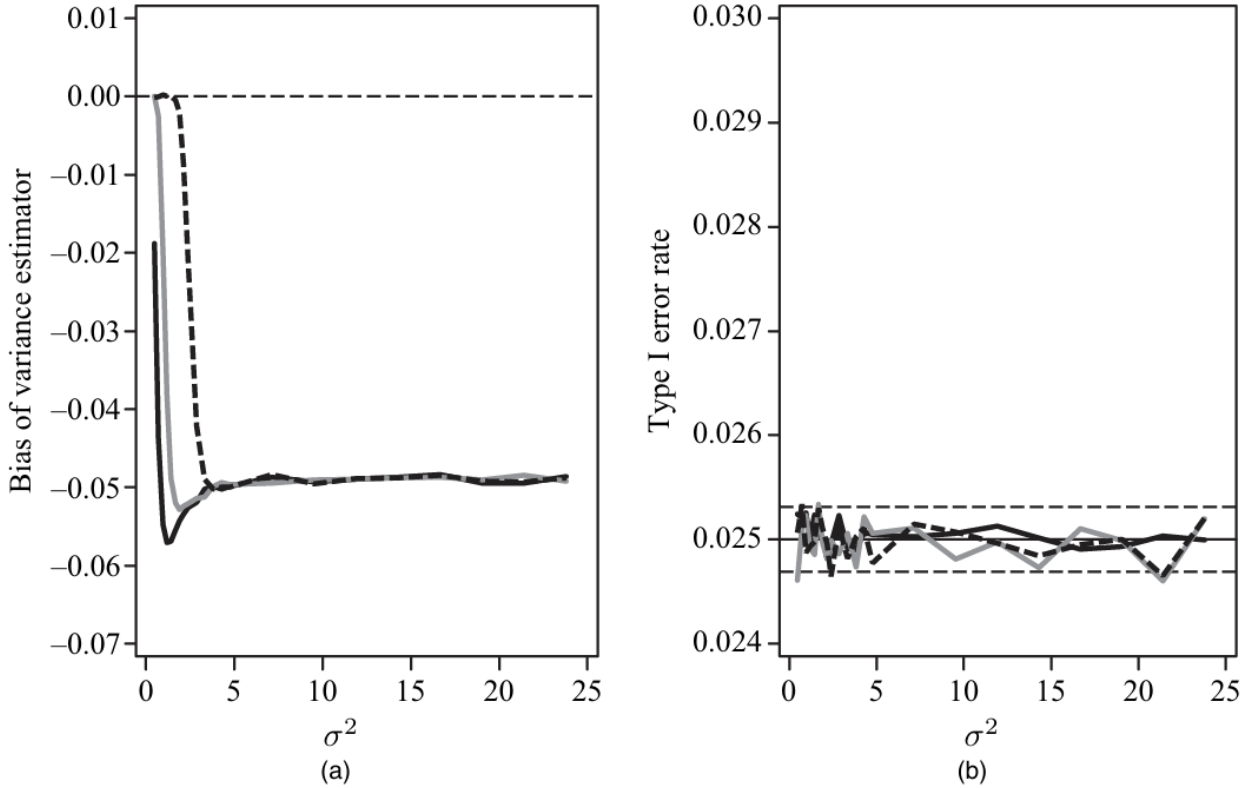

Fig. 3. (a) Bias of the variance estimator and (b) size of the *t*-test after blinded continuous monitoring for $n_1 = 10$ (———), $n_1 = 20$ (———) and $n_1 = 50$ (– – –) depending on the true variance σ^2 for nominal $\alpha = 0.025$: the broken reference lines in (b) indicate deviations from the nominal level α within twice the simulation error

Unblinded continuous monitoring

Blinded continuous monitoring

3 Asymptotic and finite-sample properties

Blinded continuous monitoring:

$$N_b = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,blind} \leq n/v\}$$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$

Fixed-sample design: $n_{req} = v\sigma^2$

Properties of N_b:

- Finite-sample results
- Asymptotic results
  - $v \to \infty$: Keep α and β fixed, it means that $\delta_a \to 0$ (The parameter under the alternative hypothesis is chosen to be as close as possible to that under the null hypothesis.)
  - $\sigma \to \infty$: Infinite variance

Finite-sample properties

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Blinded continuous monitoring: $N_b = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,blind} \leq n/v\}$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

Fixed-sample design: $n_{req} = v\sigma^2$

Theorem 1. *If the initial sample size* $n_1 \geq 2$, $0 < \sigma^2 < \infty$, *and* $0 < v < \infty$, *then we have (i)* N_b *is well-defined and* $\mathbb{P}(N_b < \infty) = 1$, *that is, the stochastic process* N_b *terminates with probability 1.*

(ii)

$$\mathbb{E}(N_b) \leq n_1 + v\sigma^2 + \frac{v(\mu_1 - \mu_2)^2}{4} = n_1 + n_{req}\left(1 + \frac{(\mu_1 - \mu_2)^2}{4\sigma^2}\right).$$

(iii)

$$\mathbb{E}(N_b^2) \leq \left(n_1 + v\sigma^2 + \frac{v(\mu_1 - \mu_2)^2}{4}\right)^2 = \left(n_1 + n_{req}\left(1 + \frac{(\mu_1 - \mu_2)^2}{4\sigma^2}\right)\right)^2$$

Upper bound

Asymptotic results

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Blinded continuous monitoring: $N_b = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,blind} \leq n/v\}$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

Fixed-sample design: $n_{req} = v\sigma^2$

The following asymptotic property of the blinded continuous monitoring (1) highlights its conservative nature. It is unlikely to underestimate n_{req}, as $\sigma \to \infty$ or $v \to \infty$.

Theorem 2. *For every ε in $(0,1)$, if the initial sample size $n_1 \geq 2$, then $\mathbb{P}(N_b \leq \varepsilon n_{req}) = \mathcal{O}((n_{req})^{-(n_1-1)})$ as $\sigma \to \infty$ or $v \to \infty$.*

Asymptotic results

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Blinded continuous monitoring: $N_b = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,blind} \leq n/v\}$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

Fixed-sample design: $n_{req} = v\sigma^2$

Theorem 3. *(i) N_b is well-defined and non-decreasing as a function of σ. Furthermore, we have $N_b(\sigma) \to \infty$ almost surely as $\sigma \to \infty$, and $\mathbb{E}(N_b) \to \infty$ as $\sigma \to \infty$.*

(ii)

$$\lim_{\sigma\to\infty} \frac{N_b}{n_{req}} = 1 \quad almost\ surely.$$

(iii)

$$\lim_{\sigma\to\infty} \mathbb{E}\left(\frac{N_b}{n_{req}}\right) = 1.$$

(iv)

$$\lim_{\sigma\to\infty} \mathbb{E}\left(\frac{N_b^2}{n_{req}^2}\right) = 1.$$

(v) As $\sigma \to \infty$, we have

$$\frac{N_b - n_{req}}{\sqrt{n_{req}}} \xrightarrow{d} N(0,1).$$

Theorem 4. *(i) N_b is well-defined and non-decreasing as a function of v. Furthermore, we have $N_b(v) \to \infty$ almost surely as $v \to \infty$, and $\mathbb{E}(N_b) \to \infty$ as $v \to \infty$.*

(ii)

$$\lim_{v\to\infty} \frac{N_b}{n_{req}} = 1 + \frac{(\mu_1 - \mu_2)^2}{4\sigma^2} \quad almost\ surely.$$

(iii)

$$\lim_{v\to\infty} \mathbb{E}\left(\frac{N_b}{n_{req}}\right) = 1 + \frac{(\mu_1 - \mu_2)^2}{4\sigma^2}.$$

(iv)

$$\lim_{v\to\infty} \mathbb{E}\left(\frac{N_b^2}{n_{req}^2}\right) = \left(1 + \frac{(\mu_1 - \mu_2)^2}{4\sigma^2}\right)^2.$$

(v) As $v \to \infty$, we have

$$\frac{N_b - n_{req}(1 + (\mu_1 - \mu_2)^2/(4\sigma^2))}{\sqrt{n_{req}}} \xrightarrow{d} N\left(0, \frac{4\sigma^2 + 2(\mu_1 - \mu_2)^2}{4\sigma^2 + (\mu_1 - \mu_2)^2}\right).$$

Simulation

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- **Unblinded continuous monitoring:**

$$N_u = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,unblind} \leq n/v\}$$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

- **Blinded continuous monitoring:**

$$N_b = \min\{n = n_1, n_1 + 1, \ldots | \hat{\sigma}^2_{n,blind} \leq n/v\}$$

where n_1 is the initial value and $v = \frac{2}{\delta_a^2}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2$.

- **Fixed-sample design:** $n_{req} = v\sigma^2$

Simulation

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Table 1: Simulations from $N(\mu_1, \sigma^2)$ and $N(\mu_2, \sigma^2)$ under 10000 runs implementing blinded and unblinded continuous monitoring of the variance ($v = 1$ and $\mu_2 = 0$ are fixed, the initial sample size $n_1 = 10$)

μ_1	n_{req}	σ	$\overline{N}_b$	$s(\overline{N}_b)$	$\overline{N}_b/n_{req}$	Upper bound[1]	$\overline{N}_u$	$s(\overline{N}_u)$	$\overline{N}_u/n_{req}$
	10	$\sqrt{10}$	11.4037	1.8735	1.1404	11.75	11.2955	1.8238	1.1296
	50	$5\sqrt{2}$	49.9064	7.3498	0.9981	51.75	49.7201	7.3623	0.9944
$\mu_1 = 1$	100	10	99.9400	10.1021	0.9994	101.75	99.5718	10.1720	0.9957
	500	$10\sqrt{5}$	500.1991	22.3504	1.0004	501.75	499.9163	22.1464	0.9998
	1000	$10\sqrt{10}$	1000.0603	31.4952	1.0001	1001.75	999.9493	31.5001	0.9999
	10	$\sqrt{10}$	11.9195	2.2187	1.1920	12.5	11.2955	1.8238	1.1296
	50	$5\sqrt{2}$	50.7311	7.4199	1.0146	52.5	49.7201	7.3623	0.9944
$\mu_1 = 2$	100	10	100.6331	10.1656	1.0063	102.5	99.5718	10.1720	0.9957
	500	$10\sqrt{5}$	500.9419	22.3626	1.0019	502.5	499.9163	22.1464	0.9998
	1000	$10\sqrt{10}$	1000.8652	31.5596	1.0009	1002.5	999.9493	31.5001	0.9999
	10	$\sqrt{10}$	16.4330	3.7084	1.6433	17.75	11.2955	1.8238	1.1296
	50	$5\sqrt{2}$	56.0726	7.6538	1.1215	57.75	49.7201	7.3623	0.9944
$\mu_1 = 5$	100	10	106.0004	10.3054	1.0600	107.75	99.5718	10.1720	0.9957
	500	$10\sqrt{5}$	506.1834	22.5512	1.0124	507.75	499.9163	22.1464	0.9998
	1000	$10\sqrt{10}$	1006.0055	31.5900	1.0060	1007.75	999.9493	31.5001	0.9999

[1] The upper bound of $\mathbb{E}(N_b)$ in Theorem 1 in blinded continuous monitoring

Simulation

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Table 2: Simulations from $N(\mu_1, \sigma^2)$ and $N(\mu_2, \sigma^2)$ under 10000 runs implementing blinded and unblinded continuous monitoring of the variance ($\sigma = 1$ and $\mu_2 = 0$ are fixed, the initial sample size $n_1 = 10$)

μ_1	n_{req}	v	$\overline{N}_b$	$s(\overline{N}_b)$	$\overline{N}_b/n_{req}$	Upper bound[1]	$\overline{N}_u$	$s(\overline{N}_u)$	$\overline{N}_u/n_{req}$
$\mu_1 = 1$	10	10	13.0250	2.7759	1.3025	14	11.2955	1.8238	1.1296
	50	50	62.4143	7.9760	1.2483	64	49.7201	7.3623	0.9944
	100	100	124.9483	10.9901	1.2495	126.5	99.5718	10.1720	0.9957
	500	500	624.8957	24.2892	1.2498	626.5	499.9163	22.1464	0.9998
	1000	1000	1249.7079	34.0695	1.2497	1251.5	999.9493	31.5001	0.9999
$\mu_1 = 2$	10	10	20.2562	4.0676	2.0256	21.5	11.2955	1.8238	1.1296
	50	50	100.2653	8.7786	2.0053	101.5	49.7201	7.3623	0.9944
	100	100	200.3337	12.2293	2.0033	201.5	99.5718	10.1720	0.9957
	500	500	1000.0871	27.1989	2.0002	1001.5	499.9163	22.1464	0.9998
	1000	1000	2000.5408	38.4516	2.0005	2001.5	999.9493	31.5001	0.9999
$\mu_1 = 5$	10	10	73.3414	4.3575	7.3341	74	11.2955	1.8238	1.1296
	50	50	363.3671	9.6653	7.2673	364	49.7201	7.3623	0.9944
	100	100	725.7457	13.6278	7.2575	726.5	99.5718	10.1720	0.9957
	500	500	3626.0818	30.3324	7.2522	3626.5	499.9163	22.1464	0.9998
	1000	1000	7251.0777	42.9622	7.2511	7251.5	999.9493	31.5001	0.9999

[1] The upper bound of $\mathbb{E}(N_b)$ in Theorem 1 in blinded continuous monitoring

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Thank you for your attention!

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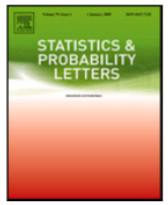

A note on blinded continuous monitoring for continuous outcomes

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ABSTRACT

Continuous monitoring is becoming more popular due to its significant benefits, including reducing sample sizes and reaching earlier conclusions. In general, it involves monitoring nuisance parameters (e.g., the variance of outcomes) until a specific condition is satisfied. The blinded method, which does not require revealing group assignments, was recommended because it maintains the integrity of the experiment and mitigates potential bias. Although Friede and Miller (2012) investigated the characteristics of blinded continuous monitoring through simulation studies, its theoretical properties are not fully explored. In this paper, we aim to fill this gap by presenting the asymptotic and finite-sample properties of the blinded continuous monitoring for continuous outcomes. Furthermore, we examine the impact of using blinded versus unblinded variance estimators in the context of continuous monitoring. Simulation results are also provided to evaluate finite-sample performance and to support the theoretical findings.

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