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Choosing the parameter of Fleming-Harrington's test in prevention randomized controlled trials - Supplementary Materials

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In this supplementary document, we provide a new proof of the theorem by Gill (1980) giving the asymptotic distribution of LR_{W_n} and we conduct a simulation study analogous to the one described in the main document, but for early effects (that is we investigate Fleming-Harrington's test with $(p \geqslant 0, q = 0)$).

1 A new proof of the asymptotic distribution of LR_{W_n}

We first recall the theorem by Gill (1980) giving the asymptotic distribution of LR_{W_n} under $\mathcal{H}_0$ and $\mathcal{H}_1$. Let $\{F_\theta : \theta \in \Theta\}$ with $\Theta \subset \mathbb{R}$ be a family of continuous cumulative distribution functions on $[0, \infty)$ indexed by a parameter $\theta \in \Theta$, and consider the following hypotheses:

$$\begin{cases} \mathcal{H}_0 & : \ F^T = F^P = F_{\theta^0}, \\ \mathcal{H}_1 & : \ F^T = F_{\theta^T} \quad \text{and} \quad F^P = F_{\theta^P}, \end{cases} \tag{1}$$

and assumptions:

Assumption 11 *There exists a function $w \in \mathbb{D}$ such that:*

$$W_n(s) \xrightarrow[n\to\infty]{a.s.} w(s).$$

Assumption 12 *There exists a^P in $]0, 1[$ and $a^T = 1 - a^P$ such that*

$$\frac{n_P}{n} \xrightarrow[n\to\infty]{} a^P \qquad \textit{and} \qquad \frac{n_T}{n} \xrightarrow[n\to\infty]{} a^T.$$

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Then the following holds:

Theorem 1 (Gill (1980)) *Let LR_{W_n} be a statistic satisfying Assumptions 11 and 12, with W_n an adapted bounded non-negative predictable process. Then under $\mathcal{H}_0$,*

$$LR_{W_n} \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}_0$$

where $\mathbb{G}_0$ is a centered Gaussian process with covariance function

$$(t_1, t_2) \to \int_0^{t_1 \wedge t_2} k^2(s) \left[\frac{a^T}{\pi^P(s)} + \frac{a^P}{\pi^T(s)} \right] (1 - \Delta\Lambda_{\theta^0}(s)) d\Lambda_{\theta^0}(s).$$

Under $\mathcal{H}_1$,

$$LR_{W_n} - \sqrt{n}\, \mu^{\mathbb{G}_1}_{(\theta^T, \theta^P)} \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}_1$$

where

$$\mu^{\mathbb{G}_1}_{(\theta^T, \theta^P)} : t \to \int_0^t k(s) \sqrt{a^T\, a^P} \left(d\Lambda_{\theta^P}(s) - d\Lambda_{\theta^T}(s) \right),$$

with

$$k(s) = w(s) \frac{\pi^P(s)\pi^T(s)}{a^P \pi^P(s) + a^T \pi^T(s)}$$

and $\mathbb{G}_1$ is a centered Gaussian process with covariance function

$$\begin{aligned}(t_1, t_2) \to \int_0^{t_1 \wedge t_2} k^2(s) \Bigg[& \frac{a^T}{\pi^P(s)} (1 - \Delta\Lambda_{\theta^P}(s)) d\Lambda_{\theta^P}(s) \\ & + \frac{a^P}{\pi^T(s)} (1 - \Delta\Lambda_{\theta^T}(s)) d\Lambda_{\theta^T}(s) \Bigg]. \end{aligned} \tag{2}$$

We propose a new alternative proof of this theorem. This new proof is more straightforward.

Preliminaries. Recall that $\mathbb{D}$ denotes the Skorokhod space of càdlàg functions (see Billingsley (1999) for details). Assume that the hypothesis $\mathcal{H}_1$ in (1) holds. Let $j = T$ if $i = P$, $j = P$ if $i = T$, and consider the processes

$$H_n^{i,j} = \sqrt{\frac{n_j}{n}} W_n \frac{n}{Y_n} \frac{Y_{n_j}^j}{n_j},$$
$$M_{n_i}^i = N_{n_i}^i - A_{n_i}^i \qquad \text{with} \qquad A_{n_i}^i = \int_0^{\cdot} Y_{n_i}^i(s) d\Lambda_{\theta^i}(s).$$

$(M_{n_i}^i)$ is a a sequence of martingales with respect to its natural filtration and $A_{n_i}^i$ is the increasing predictable process associated to $M_{n_i}^i$. Moreover, as W_n is an adapted bounded non-negative predictable process, $(H_n^{i,j})$ is a sequence of càdlàg predictable processes.

Our new proof of Theorem 1 is a consequence of the following theorem on the weak convergence of stochastic integrals and of the subsequent two lemmas.

Theorem 2 (Jakubowski et al (1989)) *Let (M_n) be a sequence of martingales, and (H_n) be a sequence of càdlàg predictable processes, such that*

1. *(M_n) satisfies the condition of uniform tightness (defined in Jakubowski et al (1989)),*
2. *$(H_n, M_n) \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} (H_\infty, M_\infty)$.*

Then

$$\int_0^{\cdot} H_n(s) dM_n(s) \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \int_0^{\cdot} H_\infty(s) dM_\infty(s).$$

Lemma 1 *Let $j = T$ if $i = P$, and $j = P$ if $i = T$. We have:*

$$H_n^{i,j} = \sqrt{\frac{n_j}{n}} W_n \frac{n}{Y_n} \frac{Y_{n_j}^j}{n_j} \xrightarrow[n\to\infty]{a.s.} \sqrt{a^j}\, \frac{k}{\pi^i}.$$

Proof of Lemma 1. This result follows from Assumptions 11 and 12 and from the fact that for $i = P, T$, by the law of large numbers,

$$\sup_{t\in\mathbb{R}^+}\left|\frac{Y^i_{n_i}}{n_i}(t) - \pi^i(t)\right| \xrightarrow[n\to\infty]{a.s.} 0. \tag{3}$$

□

Lemma 2 *For $i = T, P$, we have:*

$$\frac{M^i_{n_i}}{\sqrt{n_i}} \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \mathbb{M}^i,$$

where $\mathbb{M}^i$ is a centered Gaussian martingale with covariance function

$$(t_1, t_2) \to \operatorname{cov}(\mathbb{M}^i(t_1), \mathbb{M}^i(t_2)) = \int_0^{t_1\wedge t_2} (1 - \Delta\Lambda_{\theta^i}(s))\pi^i(s-)d\Lambda_{\theta^i}(s).$$

Proof of Lemma 2. This follows by applying Lemma 1 of Dauxois (1999). □

We now turn to the core of our new proof of Theorem 1.

Proof of Theorem 1. Let $t \in [0, \tau]$ and let $j = T$ if $i = P$ and $j = P$ if $i = T$. We decompose $LR_{W_n}(t)$ as:

$$LR_{W_n}(t) = LRM^P_{W_n}(t) - LRM^T_{W_n}(t) + LRC^P_{W_n}(t) - LRC^T_{W_n}(t)$$

where

$$LRM^i_{W_n}(t) = \int_0^t \sqrt{\frac{n_j}{n}} W_n(s)\frac{n}{Y_n(s)}\frac{Y^j_{n_j}(s)}{n_j}\frac{dM^i_{n_i}(s)}{\sqrt{n_i}}, \tag{4}$$

$$LRC^i_{W_n}(t) = \sqrt{n}\int_0^t W_n(s)\frac{n}{Y_n(s)}\frac{Y^i_{n_i}(s)}{n_i}\frac{Y^j_{n_j}(s)}{n_j}\sqrt{\frac{n_i n_j}{n\,n}}\left(d\Lambda_{\theta^i}(s) - d\Lambda_{\theta^0}(s)\right). \tag{5}$$

We consider first the convergence of (4). Note that (4) is a stochastic integral with respect to the martingale $M^i_{n_i}$, and that the jumps of $H^{i,j}_n$ are the same as those of $M^i_{n_i}$. Thus, it follows from Lemmas 1 and 2 that

$$\left(H^{i,j}_{n_i}, \frac{M^i_{n_i}}{\sqrt{n_i}}\right) \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \left(\sqrt{a^j}\,\frac{k}{\pi^i}, \mathbb{M}^i\right).$$

Moreover, the sequence $\left(\frac{M^i_{n_i}}{\sqrt{n_i}}\right)$ is uniformly tight, as a consequence of Proposition 3.2 of Jakubowski et al (1989). An application of Theorem 2 thus yields:

$$LRM^i_{W_n} \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}^i = \int_0^{\cdot} \sqrt{a^j}\,\frac{k(s)}{\pi^i(s)} d\mathbb{M}^i(s).$$

The limit $\mathbb{G}^i$ is expressed as a stochastic integral of a deterministic process with respect to a Gaussian martingale. $\mathbb{G}^i$ is thus a centered Gaussian process, with covariance function

$$(t_1, t_2) \to \int_0^{t_1\wedge t_2} a^j\,k^2(s)\,\frac{1}{(\pi^i(s))^2}(1 - \Delta\Lambda_{\theta^i}(s))\pi^i(s-)d\Lambda_{\theta^i}(s).$$

Now, the processes $\mathbb{G}^T$ and $\mathbb{G}^P$ are independent and thus, after some algebra, we have that

$$LRM^P_{W_n} - LRM^T_{W_n} \xrightarrow[n\to\infty]{\mathcal{L}(\mathbb{D})} \mathbb{G}_1 \tag{6}$$

where $\mathbb{G}_1$ is a centered Gaussian process, whose covariance function is given by (2).

We now turn to the convergence of (5). First, from Assumption 12 and the convergence (3), it is easily seen that

$$W_n(s)\frac{n}{Y_n(s)}\frac{Y^i_{n_i}(s)}{n_i}\frac{Y^j_{n_j}(s)}{n_j}\sqrt{\frac{n_i n_j}{n\,n}} \xrightarrow[n\to\infty]{a.s} \sqrt{a^T a^P}\,k(s)$$

and thus

$$\frac{1}{\sqrt{n}}\,LRC^i_{W_n} \xrightarrow[n\to\infty]{a.s} \int_0^{\cdot} \sqrt{a^T a^P}\,k(s)\left(d\Lambda_{\theta^i}(s) - d\Lambda_{\theta^0}(s)\right).$$

It follows from the definition (1) of $\mu^{\mathbb{G}_1}_{(\theta^T,\theta^P)}$ that

$$LRC^P_{W_n} - LRC^T_{W_n} - \sqrt{n}\,\mu^{\mathbb{G}_1}_{(\theta^T,\theta^P)} \xrightarrow[n\to\infty]{a.s} 0,$$

and thus,

$$LRC^P_{W_n} - LRC^T_{W_n} - \sqrt{n}\,\mu^{\mathbb{G}_1}_{(\theta^T,\theta^P)} \xrightarrow[n\to\infty]{\mathbb{P}} 0. \tag{7}$$

Finally, since

$$\begin{aligned} &LR_{W_n} - \sqrt{n}\mu^{\mathbb{G}_1}_{(\theta^T,\theta^P)} \\ &\quad = (LRM^P_{W_n} - LRM^T_{W_n}) + (LRC^P_{W_n} - LRC^T_{W_n} - \sqrt{n}\mu^{\mathbb{G}_1}_{(\theta^T,\theta^P)}), \end{aligned}$$

Theorem 1 follows from (6) and (7). □

2 Fleming-Harrington's tests for early effects ($p \geqslant 0$ and $q = 0$)

The Figure 1 reports the results of a similar study as these of the main document for the early-effects case (with $q = 0$, $p = 0, 1, 2, 3, 4$). Table 1 and 2 ar results of similar simulations as these of the main document in the early-effects case (with $q_S = 0$, $p_S = 3$ and $p_T \leqslant 10$, and with $q_S = 0$, $p_S \leqslant 5$ and $p_T \leqslant 5$).

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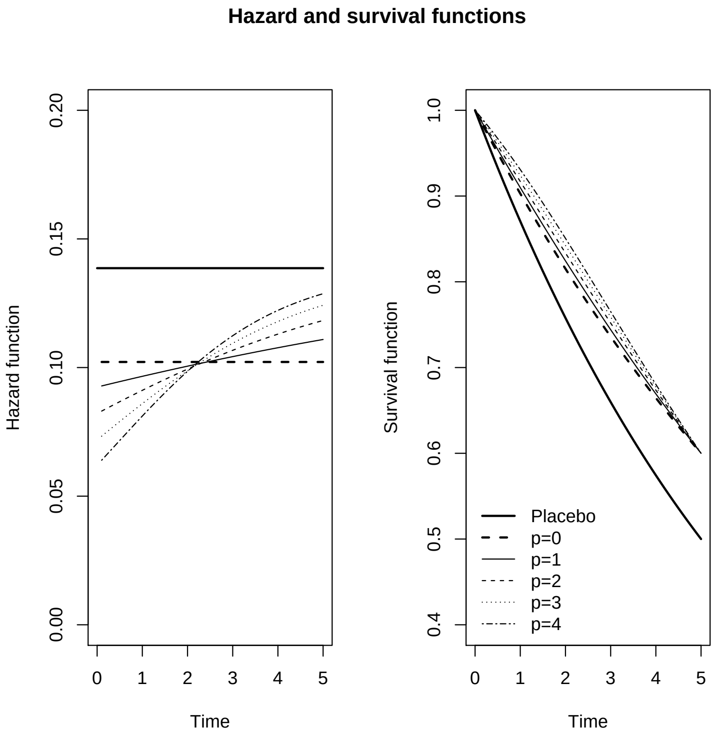

Fig. 1 Hazard and survival functions for $p \geqslant 0$ and $q = 0$. The curves $p = 0, 1, 2, 3, 4$ correspond to the hazard and survival functions in the treatment group in the condition of optimality.

Table 1 Empirical power (in %) of Fleming-Harrington's test for different values of p_T from data simulated with $p_S = 3$. The values in bold represent the maximum over the lines.

n	c	r	$p_T = 0$	$p_T = 1$	$p_T = 2$	$p_T = 3$	$p_T = 4$	$p_T = 5$	$p_T = 6$	$p_T = 7$	$p_T = 8$	$p_T = 9$	$p_T = 10$
500	0.2	0.1	89	97	98	**99**	**99**	98	98	98	97	97	96
		0.2	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
		0.3	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	0.5	0.1	23	26	28	**29**	**29**	28	26	26	25	24	23
		0.2	70	74	77	**78**	77	77	75	73	71	69	67
		0.3	95	**97**	**97**	**97**	**97**	**97**	**97**	96	95	94	93
	0.8	0.1	**9**	**9**	**9**	**9**	**9**	**9**	**9**	8	8	8	8
		0.2	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**21**	20	19	19
		0.3	42	43	43	**44**	43	42	42	41	41	39	39
1000	0.2	0.1	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	999
		0.2	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
		0.3	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	0.5	0	44	49	52	**53**	52	51	48	46	44	43	41
		0.2	94	96	**98**	**98**	**98**	97	97	95	94	94	92
		0.3	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	0.8	0.1	14	14	14	14	**15**	14	14	14	13	14	13
		0.2	40	40	**41**	**41**	40	40	40	39	38	38	37
		0.3	71	72	**73**	**73**	**73**	72	72	72	71	70	69

n	c	r	$p_T = 0$	$p_T = 1$	$p_T = 2$	$p_T = 3$	$p_T = 4$	$p_T = 5$	$p_T = 6$	$p_T = 7$	$p_T = 8$	$p_T = 9$	$p_T = 10$
2000	0.2	0.1	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	999
		0.2	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
		0.3	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	0.5	0.1	71	77	**80**	**80**	79	78	76	74	73	70	68
		0.2	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
		0.3	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	0.8	0.1	22	**23**	**23**	**23**	**23**	22	22	22	21	21	21
		0.2	66	**67**	**67**	66	66	66	65	64	63	63	61
		0.3	**95**	**95**	**95**	**95**	**95**	**95**	**95**	94	94	93	93

Table 2 Empirical power (in %) of Fleming-Harrington's test for different values of p_T from data simulated under various p_S ($n = 2000$, $c = 0.8$, $r = 0.2$). The values in bold represent the maximum over the lines.

p_S	$p_T = 0$	$p_T = 1$	$p_T = 2$	$p_T = 3$	$p_T = 4$	$p_T = 5$	$p_T = 6$	$p_T = 7$	$p_T = 8$	$p_T = 9$	$p_T = 10$
0	**64**	63	62	62	61	60	59	58	55	54	52
1	65	**66**	**66**	**66**	65	64	63	63	61	60	59
2	**64**	**64**	**64**	**64**	63	63	62	61	60	59	57
3	66	67	67	**68**	**68**	67	66	66	65	64	63
4	67	68	**69**	**69**	**69**	**69**	**69**	68	67	66	65
5	66	67	67	68	**69**	**69**	68	68	68	68	67
6	66	68	69	70	70	70	**71**	70	70	70	69
7	68	69	71	71	72	**73**	**73**	**73**	**73**	**73**	**73**
8	66	68	71	72	73	74	74	**75**	74	74	74
9	66	68	70	71	72	74	74	**75**	**75**	**75**	**75**
10	66	69	71	73	75	76	77	77	77	**78**	**78**