Analysis of Poisson frequency data under a simple crossover trial

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

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Introduction

Introduction

01 The Goal of This Article

- Frequency of patient response follows the commonly-assumed Poisson distribution under a crossover design.
- Present asymptotic and exact procedures for testing non-equality, non-inferiority and equivalence.
- Develop asymptotic and exact interval estimators for evaluate.

02 Crossover Design

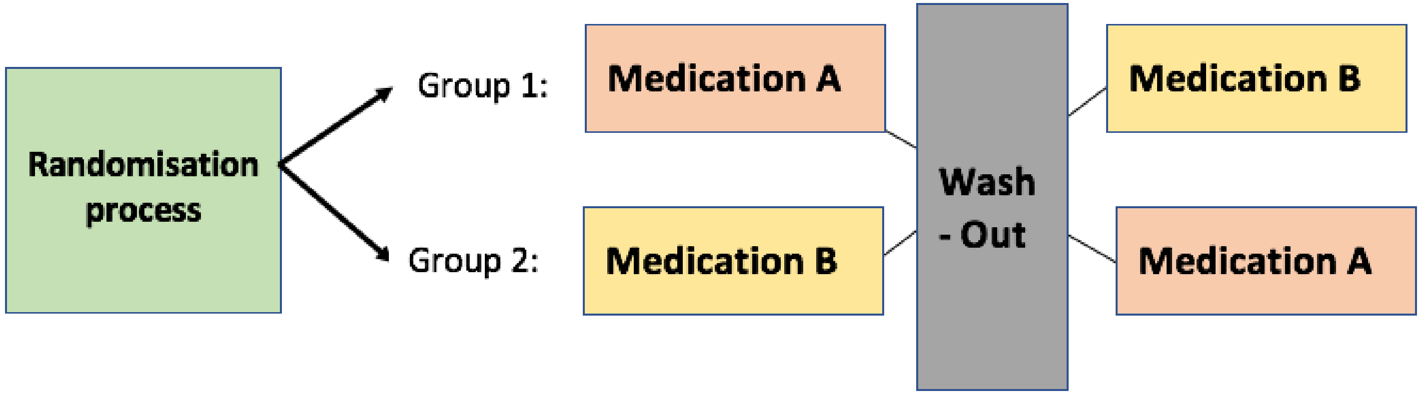
- What is crossover design?
- Advantage & Disadvantage

03 Non-equality, Non-inferiority and Equivalence

- Relationship among non-equality, non-inferiority and equivalence
- Testing for non-equality, non-inferiority and equivalence

Crossover Design

What's Crossover Design?



Treatment	Period 1	Period 2
Sequence AB	A	B
Sequence BA	B	A

Crossover Design

Advantage

- Sometimes more efficient than parallel design.
- Require fewer patients than a parallel study.
- The treatment are compared ‘within subjects’.

Disadvantage

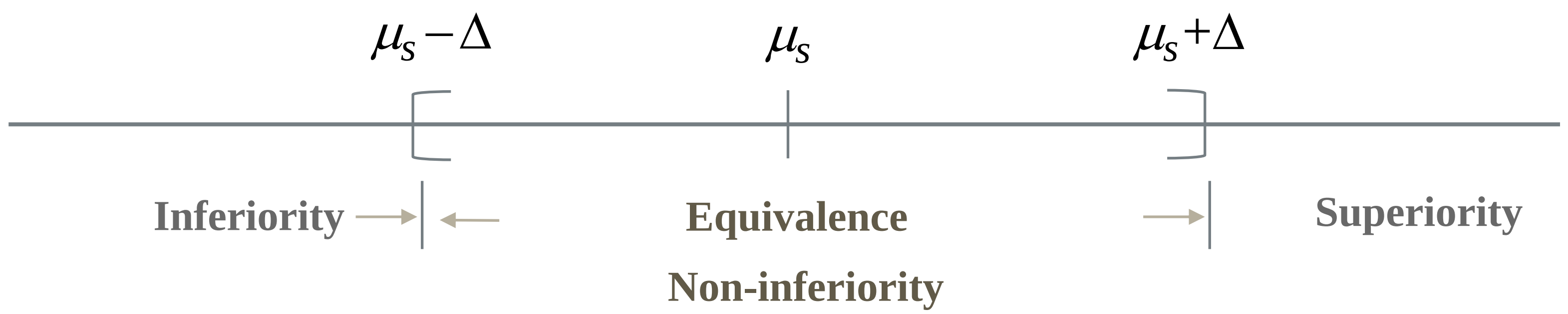
- Carryover effect
- Wash out period

Constraint

- In medical clinical trials, the disease should be chronic and stable.
- The treatments should not result in total cures but only alleviate the disease condition.

Non-equality、Non-inferiority and Equivalence

Relationship among non-inferiority, superiority, and equivalence



$$H_0: \mu_t - \mu_s \le -\Delta$$
$$H_a: \mu_t - \mu_s > -\Delta$$

$$H_0: |\mu_t - \mu_s| \ge \Delta$$
$$H_a: |\mu_t - \mu_s| < \Delta$$

$$H_0: \mu_t - \mu_s \le \Delta$$
$$H_a: \mu_t - \mu_s > \Delta$$

Ref : https://ntuhmc.ntuh.gov.tw/epaper-70th.htm

Contribution

- Present asymptotic and exact procedures for testing non-equality, non-inferiority and equivalence.
- Develop asymptotic and exact interval estimators for evaluate.
- Provide asymptotic and exact test procedures to do testing no matter sample size is small, moderate or large.
- Asymptotic interval estimator with logarithmic transform will be more precise than exact interval estimator.

Notation, model assumption and methods

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Notation

Y_{ist} -frequency of the response on patient I assigned to sequence s at period t

patient $i=1,\ldots,n_s$ sequence $s=1,\ 2$ period $t=1,\ 2$

X_{ist} -covariate of treatment receipt

$$x_{ist}=\begin{cases}1, & \text{treatment B}\\ 0, & o.w.\end{cases}$$

Z_{it} -covariate of period

$$z_{it}=\begin{cases}1, & \text{period 2}\\ 0, & o.w.\end{cases}$$

$$Y_{ist} \sim Poisson(E(Y_{ist})) \qquad E(Y_{ist})=u_{is}\exp(x_{ist}\eta+z_{it}\gamma)$$

u_{is} -the effect due to the underlying characteristics of the $\boldsymbol{i^{th}}$ patient assigned to sequence s

η -the effect of treatment B relative to treatment A

γ -the effect for period 2 v.s. period 1

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Model assumption

$$Y_{i12} | Y_{i1+} = y_{i1+} \sim Bin(y_{i1+}, \exp(\eta+\gamma)/(1+\exp(\eta+\gamma)))$$

$$P(Y_{+12} = y_{+12} | \underset{\sim}{y}_{1+}, \eta, \gamma) = \binom{y_{+1+}}{y_{+12}} p_1^{y_{+12}} (1-p_1)^{y_{+1+}-y_{+12}}$$

$$Y_{+12} (= \sum_{i=1}^{n_1} Y_{i12}) \qquad \underset{\sim}{y}'_{1+} = (y_{11+}, y_{21+}, \ldots, y_{n_1 1+}) \qquad y_{+1+} = \sum_{i=1}^{n_1} y_{i1+} \qquad p_1 = \exp(\eta+\gamma)/(1+\exp(\eta+\gamma))$$

$$Y_{i22} | Y_{i2+} = y_{i2+} \sim Bin(y_{i2+}, \exp(\gamma)/(\exp(\eta)+\exp(\gamma)))$$

$$P(Y_{+22} = y_{+22} | \underset{\sim}{y}_{2+}, \eta, \gamma) = \binom{y_{+2+}}{y_{+22}} p_2^{y_{+22}} (1-p_2)^{y_{+2+}-y_{+22}}$$

$$Y_{+22} (= \sum_{i=1}^{n_2} Y_{i22}) \qquad \underset{\sim}{y}'_{2+} = (y_{12+}, y_{22+}, \ldots, y_{n_2 2+}) \qquad y_{+2+} = \sum_{i=1}^{n_2} y_{i2+} \qquad p_2 = \exp(\gamma)/(\exp(\eta)+\exp(\gamma))$$

Conditional MLE of p_s is $\hat{p}_s = \frac{y_{+s2}}{y_{+s+}}$, $(s = 1, 2)$

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Model assumption

$$RM_T = \exp(\eta)$$

given a fixed period, the ratio of two mean frequencies of responses on a given patient between treatment B and A

$$RM_P = \exp(\gamma)$$

given a fixed treatment, the ratio of two mean frequencies for period 2 versus period 1 on a given patient

Conditional MLE of p_s is $\hat{p}_s = \frac{y_{+s2}}{y_{+s+}}$ $,(s = 1,2)$

$$RM_T^2 = p_1(1-p_2)/p_2(1-p_1)$$

$$Var(\log(RM_T)) = \frac{1}{4}\left(\frac{1}{y_{+1+}p_1(1-p_1)} + \frac{1}{y_{+2+}p_2(1-p_2)}\right)$$

$$RM_T = \left(\frac{\hat{p}_1(1-\hat{p}_2)}{\hat{p}_2(1-\hat{p}_1)}\right)^{1/2} = \left(\frac{Y_{+12}Y_{+21}}{Y_{+11}Y_{+22}}\right)^{1/2}$$

$$Var(\log(RM_T)) = \frac{1}{4}\left(\frac{1}{Y_{+12}} + \frac{1}{Y_{+11}} + \frac{1}{Y_{+21}} + \frac{1}{Y_{+22}}\right)$$

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Methods-Fieller's Theorem

- For skewed distribution, use delta method we may obtained asymmetric confidence limits.
- While $o_p(1)$ is small, then the large-sample confidence limits will be close to those given by Fieller's theorem.

Assuming that $\mathbf{L}'\boldsymbol{\theta} \neq 0$,we must have

$$\frac{t^2\hat{\sigma}^2[\mathbf{L}'\mathbf{I}^{-1}(\boldsymbol{\theta})\mathbf{L}]}{(\mathbf{L}'\hat{\boldsymbol{\theta}})^2} = o_p(1)$$

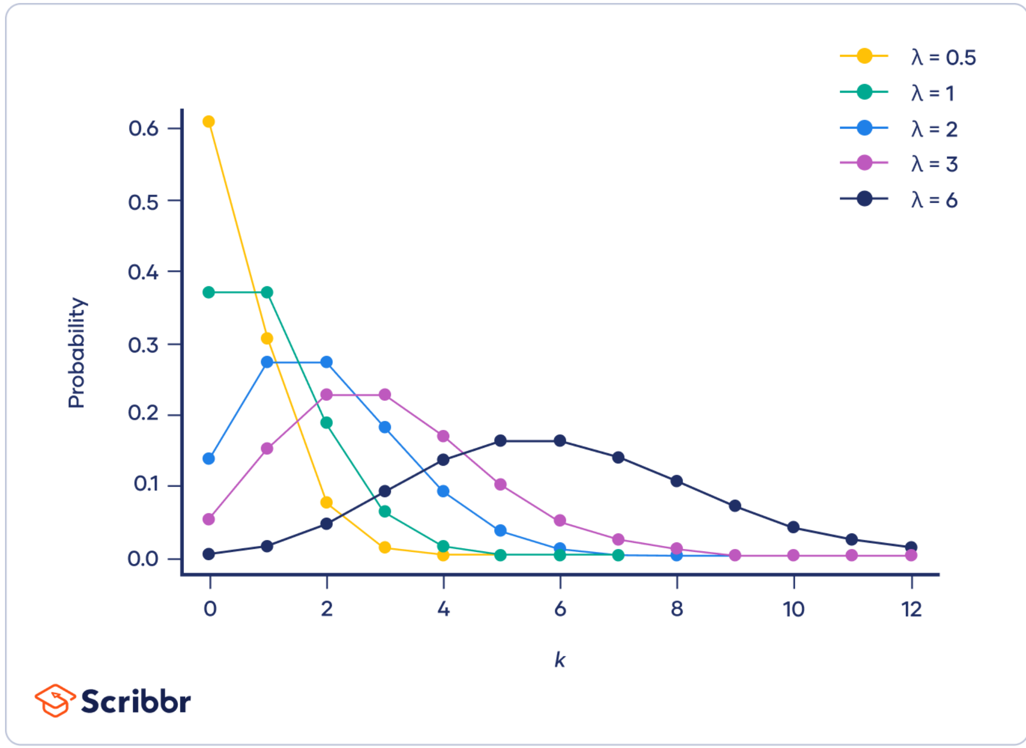
t : the appropriate percentile of the t-distribution

Let $\boldsymbol{g}(\boldsymbol{\theta}) = (g_1(\boldsymbol{\theta}), \ \dots \ , g_l(\boldsymbol{\theta}))^T$

Partial derivatives $\mathbf{L} = [\frac{\partial g_l(\boldsymbol{\theta})}{\partial \theta_j}], \ i = 1, \dots, l; \ j = 1, \dots, k$

$$\sqrt{n}(\boldsymbol{g}(\hat{\boldsymbol{\theta}}_n) - \boldsymbol{g}(\boldsymbol{\theta})) \to MN_l(0, \mathbf{L}'\mathbf{I}^{-1}(\boldsymbol{\theta})\mathbf{L}) \ as \ n \to \infty$$

$$\mathbf{I}^{-1}(\boldsymbol{g}(\boldsymbol{\theta})) = [\mathbf{L}'\mathbf{I}^{-1}(\boldsymbol{\theta})\mathbf{L}]^{-1}$$



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Methods-Fisher Exact Test

	Guess		
Actually	Milk	Tea	
Milk	n_{11}	n_{12}	n_{1+}
Tea	n_{21}	n_{22}	n_{2+}
	n_{+1}	n_{+2}	n_{++}

H_0: *the variables are independent*

H_a: *the variables are dependent*

Reject H_0 if

$$P(X \ge n_{11} \mid n_{+1} = n_{+2} = n_{1+} = n_{2+}) = \sum_{X \ge n_{11}} \binom{n_{1+}}{n_{11}} \binom{n_{2+}}{n_{+1} - n_{11}} \Big/ \binom{n_{++}}{n_{+1}} \le \alpha$$

Methods

Test non-equality

$$H_0 : \eta = 0 \ (RM_T = 1),\ H_1 : \eta \neq 0 \ (RM_T \neq 1)$$

Reject $\boldsymbol{H_0}$ at the $\boldsymbol{\alpha}$-level if

$$\log(RM_T) / \sqrt{Var_{H_0}(\log(RM_T))} > Z_{\alpha/2} \text{ or } \log(RM_T) / \sqrt{Var_{H_0}(\log(RM_T))} < -Z_{\alpha/2} \qquad \textbf{(7)}$$

where $$Var_{H_0}(\log(RM_T)) = (1/y_{+1+} + 1/y_{+2+}) / [4\hat{\bar{p}}(1-\hat{\bar{p}})],\ \hat{\bar{p}} = (Y_{+12} + Y_{+22}) / (y_{+1+} + y_{+2+})$$

To alleviate the concern of our inference directly based on the possibly skewed distribution of RM_T

By Filler's Theorem

$$Z(\psi_T) = \hat{p}_1(1-\hat{p}_2) - \psi_T \hat{p}_2(1-\hat{p}_1), \text{ where } \psi_T = RM_T^2, \text{ and } E(Z(\psi_T)) = 0$$

$$Var(Z(\psi_T)) = Var(\hat{p}_1(1-\hat{p}_2)) + \psi_T^2 Var(\hat{p}_2(1-\hat{p}_1)) - 2\psi_T Cov(\hat{p}_1(1-\hat{p}_2), \hat{p}_2(1-\hat{p}_1))$$

Reject $\boldsymbol{H_0}$ at the $\boldsymbol{\alpha}$-level if

$$Z(1) / \sqrt{Var_{H_0}(Z(1))} > Z_{\alpha/2} \text{ or } Z(1) / \sqrt{Var_{H_0}(Z(1))} < -Z_{\alpha/2} \qquad \textbf{(9)}$$

Methods

Test non-equality

$$H_0 : \eta = 0\ (RM_T = 1),\ H_1 : \eta \neq 0\ (RM_T \neq 1)$$

Two Sample T-Test

Given the total $\boldsymbol{y_{+s+}}$ being reasonably large for both $\boldsymbol{s}$, reject $\boldsymbol{H_0}$ at the $\boldsymbol{\alpha}$-level if

$$(\hat{p}_1 - \hat{p}_2)/\sqrt{\hat{\bar{p}}(1-\hat{\bar{p}})(1/y_{++1} + 1/y_{++2})} > Z_{\alpha/2}, \text{ or}$$
$$(\hat{p}_1 - \hat{p}_2)/\sqrt{\hat{\bar{p}}(1-\hat{\bar{p}})(1/y_{++1} + 1/y_{++2})} < -Z_{\alpha/2}. \quad \textbf{(10)}$$

where $\hat{\bar{p}} = (Y_{+12} + Y_{+22})/(y_{+1+} + y_{+2+})$

Fisher Exact Test

$$P(Y_{+12} \geq y_{+12} \mid y_{++2}, \underset{\sim}{y}_{1+}, \underset{\sim}{y}_{2+}, RM_T = 1) = \sum_{y \geq y_{+12}} \binom{y_{+1+}}{y}\binom{y_{+2+}}{y_{++2} - y} \Big/ \binom{y_{+++}}{y_{++2}} \leq \alpha/2 \ or \quad \textbf{(13)}$$
$$P(Y_{+21} \geq y_{+21} \mid y_{++2}, \underset{\sim}{y}_{1+}, \underset{\sim}{y}_{2+}, RM_T = 1) = \sum_{y \leq y_{+12}} \binom{y_{+1+}}{y}\binom{y_{+2+}}{y_{++2} - y} \Big/ \binom{y_{+++}}{y_{++2}} \leq \alpha/2$$

$$\underset{\sim}{y}'_{1+} = (y_{11+}, y_{21+}, \ldots, y_{n_1 1+}) \qquad \underset{\sim}{y}'_{2+} = (y_{12+}, y_{22+}, \ldots, y_{n_2 2+})$$

Methods

Test non-inferiority

$$H_0: RM_T \le RM_l (0 < RM_l < 1),\ H_1: RM_T > RM_l$$

Reject $\boldsymbol{H_0}$ at the $\boldsymbol{\alpha}$-level and claim that treatment B is non-inferior to treatment A if the test statistic

$$(\log(RM_T) - \log(RM_l)) / \sqrt{Var(\log(RM_T))} > Z_\alpha \quad \textbf{(14)}$$

$$Z(\psi_l) / \sqrt{Var(Z(\psi_l))} > Z_\alpha, \text{ where } \psi_l = RM_l^2 \quad \textbf{(15)}$$

$$P(Y_{+12} \ge y_{+12} \mid y_{++2}, \underset{\sim}{y}_{1+}, \underset{\sim}{y}_{2+}, RM_l) = \sum_{y \ge y_{+12}} \binom{y_{+1+}}{y} \binom{y_{+2+}}{y_{++2} - y} (RM_l^2)^y / \sum_y \binom{y_{+1+}}{y} \binom{y_{+2+}}{y_{++2} - y} (RM_l^2)^y < \alpha \quad \textbf{(16)}$$

Methods

Test equivalence

$$H_0: RM_T \le RM_l \text{ or } RM_T \ge RM_u,\ \ H_1: RM_l < RM_T < RM_u$$

$$(\log(RM_T) - \log(RM_l)) / \sqrt{Var(\log(RM_T))} > Z_\alpha \text{ and } (\log(RM_T) - \log(RM_u)) / \sqrt{Var(\log(RM_T))} < -Z_\alpha \tag{17}$$

$$Z(\psi_l) / \sqrt{Var(Z(\psi_l))} > Z_\alpha \text{ and } Z(\psi_u) / \sqrt{Var(Z(\psi_u))} < -Z_\alpha, \text{ where } \psi_l = RM_l^2, \psi_u = RM_u^2 \tag{18}$$

$$P(Y_{+12} \ge y_{+12} \mid y_{++2}, \underset{\sim}{y}_{1+}, \underset{\sim}{y}_{2+}, RM_l) < \alpha \text{ and } P(Y_{+12} \le y_{+12} \mid y_{++2}, \underset{\sim}{y}_{1+}, \underset{\sim}{y}_{2+}, RM_u) < \alpha \tag{19}$$

Methods

Interval Estimation

$$\left[RM_T \exp(-Z_{\alpha/2})\sqrt{Var(\log(RM_T))},\ RM_T \exp(Z_{\alpha/2})\sqrt{Var(\log(RM_T))} \right] \qquad (20)$$

If $\boldsymbol{A > 0}$, $\boldsymbol{B^2 - AC > 0}$, asymptotic 100($\boldsymbol{1-\alpha}$)% confidence interval for $\boldsymbol{RM_T}$ as given by

$$\left[\max\left\{ \frac{B-\sqrt{B^2-AC}}{A},\ 0 \right\}^{1/2}, \left(\frac{B+\sqrt{B^2-AC}}{A} \right)^{1/2} \right] \qquad (22)$$

$$A = ((1-\hat{p}_1)\hat{p}_2)^2 - Z^2_{\alpha/2} Var((1-\hat{p}_1)\hat{p}_2)$$
$$B = \hat{p}_1(1-\hat{p}_2)(1-\hat{p}_1)\hat{p}_2 - Z^2_{\alpha/2} Cov(\hat{p}_1(1-\hat{p}_2),\ (1-\hat{p}_1)\hat{p}_2)$$
$$C = (\hat{p}_1(1-\hat{p}_2))^2 - Z^2_{\alpha/2} Var((1-\hat{p}_2)\hat{p}_1)$$

$$[CR_l(\alpha), CR_u(\alpha)] \qquad (23)$$

Monte Carlo Simulations and Result

Monte Carlo Simulations

Equivalence

$$Y_{ist} \sim Poisson(E(Y_{ist})),\ E(Y_{ist}) = u_{is}\exp(x_{ist}\eta + z_{it}\gamma),\ u_{is} \sim Gamma(\alpha,\beta),\ E(u_{is}) = \alpha\beta$$

Type I error

$$H_0 : \eta = 0\ (RM_T = 1),\ H_1 : \eta \neq 0\ (RM_T \neq 1)$$

$$E(u_{is}) = 1,\ 3,\ 5,\ \alpha = E(u_{is})/\beta \text{ and } \beta = 1,\ 2,\ 5$$

$$RM_P = 0.5,\ 2.0$$

$$n_1 = n_2 = 15,\ 30,\ 50$$

Power

$$H_0 : \eta = 0\ (RM_T = 1),\ H_1 : \eta \neq 0\ (RM_T \neq 1)$$

$$E(u_{is}) = 3,\ \alpha = E(u_{is})/\beta \text{ and } \beta = 1,\ 2,\ 5$$

$$RM_T = 0.5,\ 0.75,\ 1.25,\ 2.0$$

$$n_1 = n_2 = 15,\ 30,\ 50$$

$$RM_P = 0.5,\ 2.0$$

Result

Equivalence

$H_0: \eta = 0\ (RM_T = 1),\ H_1: \eta \neq 0\ (RM_T \neq 1)$ $\alpha = E(u_{is}) / \beta$ and $\beta = 1$

$RM_P = 0.50$

$E(u_{ig})$	n	(7)	(9)	(10)	(13)
1	15	0.059	0.044	0.044	0.018
	30	0.059	0.052	0.052	0.031
	50	0.055	0.051	0.051	0.034
3	15	0.056	0.053	0.053	0.033
	30	0.048	0.047	0.047	0.034
	50	0.054	0.053	0.053	0.042
5	15	0.055	0.052	0.052	0.037
	30	0.058	0.057	0.057	0.046
	50	0.050	0.049	0.049	0.042
$RM_P = 2.00$					
1	15	0.061[a]	0.053	0.053	0.032
	30	0.049	0.046	0.046	0.032
	50	0.050	0.048	0.048	0.036
3	15	0.052	0.049	0.049	0.036
	30	0.052	0.051	0.051	0.040
	50	0.050	0.050	0.050	0.043
5	15	0.055	0.053	0.053	0.043
	30	0.054	0.053	0.053	0.043
	50	0.046	0.046	0.046	0.038

Result

Equivalence

$H_0:\eta=0\ (RM_T=1),\ H_1:\eta\neq 0\ (RM_T\neq 1)$

$E(u_{is})=3,\ \alpha=E(u_{is})/\beta$ and $\beta=1$

$RM_P=0.50$					
RM_T	n	(7)	(9)	(10)	(13)
0.50	15	0.891	0.890	0.890	0.841
	30	0.994	0.994	0.994	0.991
	50	1.000	1.000	1.000	1.000
0.75	15	0.318	0.311	0.311	0.245
	30	0.548	0.545	0.545	0.488
	50	0.769	0.768	0.768	0.734
1.25	15	0.260	0.255	0.255	0.205
	30	0.452	0.450	0.450	0.399
	50	0.650	0.650	0.650	0.614
1.50	15	0.685	0.683	0.683	0.626
	30	0.932	0.932	0.932	0.914
	50	0.995	0.995	0.995	0.993
$RM_P=2.00$					
0.50	15	0.993	0.993	0.993	0.990
	30	1.000	1.000	1.000	1.000
	50	1.000	1.000	1.000	1.000
0.75	15	0.552	0.548	0.548	0.496
	30	0.839	0.838	0.838	0.811
	50	0.966	0.966	0.966	0.960
1.25	15	0.451	0.449	0.449	0.403
	30	0.737	0.736	0.736	0.708
	50	0.916	0.917	0.917	0.906
1.50	15	0.929	0.928	0.928	0.909
	30	0.998	0.998	0.998	0.997
	50	1.000	1.000	1.000	1.000

Monte Carlo Simulations

Non-inferiority

$$Y_{ist} \sim Poisson(E(Y_{ist})),\ E(Y_{ist}) = u_{is}\exp(x_{ist}\eta + z_{it}\gamma),\ u_{is} \sim Gamma(\alpha, \beta),\ E(u_{is}) = \alpha\beta$$

Type I error

$$H_0 : RM_T \le RM_l (0 < RM_l < 1),\ H_1 : RM_T > RM_l \qquad E(u_{is}) = 1,\ 3,\ 5,\ \alpha = E(u_{is})/\beta \text{ and } \beta = 1,\ 2,\ 5$$

$$RM_P = 0.5,\ 2.0,\ RM_l = 0.8 \qquad n_1 = n_2 = 15,\ 30,\ 50$$

Power

$$H_0 : RM_T \le RM_l (0 < RM_l < 1),\ H_1 : RM_T > RM_l \qquad E(u_{is}) = 1,\ 3,\ 5,\ \alpha = E(u_{is})/\beta \text{ and } \beta = 1,\ 2,\ 5$$

$$RM_T = 1.0$$

$$n_1 = n_2 = 15,\ 30,\ 50$$

$$RM_P = 0.5,\ 2.0,\ RM_l = 0.8$$

Result

Non-inferiority

$H_0: RM_T \leq RM_l (0 < RM_l < 1),\ H_1: RM_T > RM_l$

$\alpha = E(u_{is}) / \beta$ and $\beta = 1,\ 2,\ 5$

$RM_P = 0.50$				
$E(u_{ig})$	n	(14)	(15)	(16)
1	15	0.045	0.048	0.024
	30	0.051	0.048	0.030
	50	0.052	0.048	0.037
3	15	0.049	0.047	0.034
	30	0.050	0.048	0.039
	50	0.046	0.043	0.038
5	15	0.049	0.047	0.038
	30	0.052	0.049	0.042
	50	0.048	0.046	0.040
$RM_P = 2.0$				
1	15	0.047	0.045	0.028
	30	0.049	0.046	0.034
	50	0.047	0.044	0.038
3	15	0.047	0.045	0.036
	30	0.054	0.051	0.044
	50	0.053	0.052	0.045
5	15	0.049	0.047	0.040
	30	0.051	0.048	0.043
	50	0.050	0.048	0.045

Result

$H_0: RM_T \leq RM_l (0 < RM_l < 1),\ H_1: RM_T > RM_l$

$\alpha = E(u_{is}) / \beta$ and $\beta = 1$

Non-inferiority

$RM_P = 0.50$				
$E(u_{ig})$	n	(14)	(15)	(16)
1	15	0.159	0.156	0.100
	30	0.247	0.237	0.187
	50	0.354	0.338	0.294
3	15	0.329	0.315	0.268
	30	0.535	0.520	0.484
	50	0.712	0.701	0.673
5	15	0.468	0.457	0.418
	30	0.716	0.709	0.684
	50	0.891	0.886	0.877
$RM_P = 2.0$				
1	15	0.248	0.238	0.189
	30	0.401	0.388	0.343
	50	0.559	0.547	0.511
3	15	0.524	0.511	0.472
	30	0.779	0.770	0.753
	50	0.931	0.929	0.923
5	15	0.712	0.704	0.679
	30	0.928	0.924	0.917
	50	0.993	0.992	0.992

Monte Carlo Simulations and Result

Interval Estimator

$$\alpha = E(u_{is}) / \beta \text{ and } \beta = 1, 2, 5$$

$RM_P = 0.50$					
$E(u_{ig})$	RM_T	n	(20)	(22)	(23)
3	0.50	15	0.953 (0.471)	0.989 (0.644)	0.971 (0.522)
		30	0.954 (0.321)	0.990 (0.429)	0.968 (0.346)
		50	0.953 (0.245)	0.991 (0.324)	0.966 (0.260)
	1.00	15	0.951 (0.765)	0.975 (0.955)	0.967 (0.824)
		30	0.950 (0.524)	0.977 (0.630)	0.963 (0.556)
		50	0.953 (0.399)	0.979 (0.474)	0.961 (0.419)
	2.00	15	0.951 (1.329)	0.958 (1.580)	0.966 (1.372)
		30	0.949 (0.905)	0.960 (1.010)	0.960 (0.934)
		50	0.949 (0.693)	0.961 (0.758)	0.946 (0.716)
5	0.50	15	0.951 (0.354)	0.990 (0.475)	0.965 (0.385)
		30	0.948 (0.245)	0.989 (0.325)	0.960 (0.260)
		50	0.952 (0.188)	0.991 (0.249)	0.961 (0.197)
	1.00	15	0.950 (0.576)	0.976 (0.697)	0.964 (0.613)
		30	0.953 (0.400)	0.980 (0.475)	0.963 (0.420)
		50	0.946 (0.308)	0.976 (0.363)	0.955 (0.320)
	2.00	15	0.951 (1.000)	0.960 (1.127)	0.963 (1.032)
		30	0.952 (0.693)	0.963 (0.758)	0.946 (0.716)
		50	0.951 (0.532)	0.963 (0.576)	0.958 (0.540)

Monte Carlo Simulations and Result

Interval Estimator

$\alpha = E(u_{is}) / \beta$ and $\beta = 1,\ 2,\ 5$

$RM_P = 2.0$					
3	0.50	15	0.951 (0.323)	0.960 (0.351)	0.964 (0.348)
		30	0.952 (0.223)	0.964 (0.240)	0.964 (0.236)
		50	0.948 (0.172)	0.959 (0.184)	0.957 (0.179)
	1.00	15	0.951 (0.526)	0.955 (0.558)	0.962 (0.558)
		30	0.948 (0.365)	0.953 (0.381)	0.956 (0.382)
		50	0.950 (0.280)	0.956 (0.291)	0.958 (0.290)
	2.00	15	0.951 (0.913)	0.949 (0.966)	0.963 (0.942)
		30	0.952 (0.632)	0.953 (0.652)	0.948 (0.652)
		50	0.951 (0.485)	0.952 (0.496)	0.957 (0.488)
5	0.50	15	0.955 (0.246)	0.964 (0.265)	0.965 (0.260)
		30	0.950 (0.172)	0.963 (0.184)	0.960 (0.179)
		50	0.951 (0.132)	0.963 (0.142)	0.958 (0.137)
	1.00	15	0.952 (0.401)	0.957 (0.420)	0.961 (0.421)
		30	0.951 (0.280)	0.957 (0.290)	0.958 (0.290)
		50	0.950 (0.216)	0.957 (0.224)	0.957 (0.222)
	2.00	15	0.951 (0.696)	0.952 (0.722)	0.949 (0.719)
		30	0.953 (0.485)	0.953 (0.496)	0.958 (0.489)
		50	0.951 (0.375)	0.951 (0.381)	0.955 (0.383)

Application

An Example

01

Double-Blind Crossover Trial for Asthma patients

Treatment A：Placebo

Treatment B：Beta-agonist salmeterol (50g twice daily)

02

101 participate only 87 patients who completed the trial

Randomized to sequence AB or sequence BA

Sequence AB	**24 weeks placebo**	Washeout period	**24 weeks salmeterol**
		4 weeks	
Sequence BA	**24 weeks salmeterol**	Washeout period	**24 weeks placebo**

An Example

Sums of exacerbations in asthma on the 87 patients

$Y_{+11} = 15,\ Y_{+12} = 6$ for sequence 1 ; $Y_{+21} = 14,\ Y_{+22} = 23$ for sequence 2 $\quad RM_T = 0.493$

Test non-equality	(7)	(9)	(10)	(13)
P-value	0.010	0.014	0.014	0.028

All these suggest that there be significant evidence that taking salmeterol at the 5% level can reduce the mean number of exacerbations in asthma.

Test non-equality	(20)	(22)	(23)
95% confidence interval	[0.227, 0.880]	[0.167, 0.931]	[0.252, 0.937]

Discussions

Discussions

- Asymptotic interval estimators for large sample, exact interval estimator can be use of small sample.
- Asymptotic test procedures can all perform well with respect to the estimated Type I error as n=15, but power is larger than exact test procedures.
- The interval estimator (20) based on $\widehat{RM}_T$ with the logarithmic transformation is probably the best among the three interval estimators discussed here.

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Thanks!