STAT 6390 HOMEWORK 5
Sequential Methods in Clinical Trials

① (a) 99% RCI $= \left[Z_k \pm C_k(\alpha)\right] / \sqrt{I_k}$

where $C_k(\alpha) = C_k(0.01) = 2.939$

$I_k = Var^{-1}(\bar{x} - \bar{y}) = \dfrac{mk}{2\sigma^2} = \dfrac{mk}{2}$

where $m = \dfrac{2}{K} I_K = \dfrac{2}{K} R\, I_{f,2} = \dfrac{2}{K} R \left(\dfrac{\phi^{-1}(1-\alpha/2) + \phi^{-1}(1-\beta)}{\delta} \right)^2$

$m = \dfrac{2}{4}(1.152)\left(\dfrac{2.576 + 1.28}{0.5}\right)^2 = 34.25$

$\Rightarrow$ the group size was $\underline{35}$, so $I_k = 17.5k$

$RCI_1 = [2.39 \pm 2.939]/\sqrt{17.5} = .57 \pm .70 = [-.13, 1.27]$

$RCI_2 = [1.33 \pm 2.939]/\sqrt{35} = .22 \pm .50 = [-.28, .72]$

$RCI_3 = [1.69 \pm 2.939]/\sqrt{52.5} = .23 \pm .41 = [-.18, .64]$

$RCI_4 = [2.88 \pm 2.939]/\sqrt{70} = .34 \pm .35 = [-.01, .69]$

(b) Test $H_0: \mu_A = \mu_B$ vs $H_A: \neq$.

If $RCI_k \subset [-.5, .5] \Rightarrow$ stop, accept H_0

If $RCI_k \cap [-.5, .5] = \phi \Rightarrow$ stop, reject H_0.

Cannot accept or reject H_0 until $k = K = 4$.
Then, since H_0 is still not rejected,
<u>accept H_0</u>. That is approach #1.

Second approach. Construct $(1-2\beta) = (1-0.2)$ RCI.
However, we don't have a Pocock table (2.1) for $\alpha = 0.2$. For this reason only, let us design an RCI-based test with power $1-\beta = 0.95$ instead of 0.9 (after all, the power for the test in #16 is not specified).

Then $1-2\beta = 0.9$; $C_k(2\beta) = 2.067$, and

$RCI(1-2\beta) = [Z_k \pm 2.067]/\sqrt{17.5k}$

$RCI_1(1-2\beta) = [2.39 \pm 2.067]/\sqrt{17.5} = .57 \pm .49 = [.08, 1.06]$

$RCI_2(1-2\beta) = [1.33 \pm 2.067]/\sqrt{35} = .22 \pm .35 = [-.13, .57]$

$RCI_3(1-2\beta) = [1.69 \pm 2.067]/\sqrt{52.5} = .23 \pm .29 = [-.06, .52]$

$RCI_4(1-2\beta) = [2.88 \pm 2.067]/\sqrt{70} = .34 \pm .25 = [-.09, .59]$

If $RCI_k(1-2\beta) \subset [-.5, .5]$ $\Rightarrow$ accept H_0.

If $0 \notin RCI_k(1-\alpha)$ $\Rightarrow$ reject H_0.

None of these are satisfied, and the group size has not been selected large enough to guarantee a clear decision @ $k=K$.

We have not rejected H_0 $\Rightarrow$ @ $k=4$, accept H_0.

By the way, the parent test (Pocock) rejecting H_0 when $|Z_k| > 2.939$ will also accept H_0 @ $\alpha = 0.01$.

(2) For the OBF test, $C_K(\alpha) = 2.609\sqrt{\frac{K}{k}} = \frac{5.218}{\sqrt{k}}$

and $m = \frac{2}{4}(1.010)\left(\frac{2.576 + 1.28}{0.5}\right)^2 = 30.03$

$\Rightarrow$ the group size was 31, so $I_k = 15.5k$.

(a) $RCI_1 = [2.39 \pm 5.218]/\sqrt{15.5} = .61 \pm 1.33 = [-.72, 1.94]$

$RCI_2 = [1.33 \pm 3.69]/\sqrt{31} = .24 \pm .66 = [-.42, .90]$

$RCI_3 = [1.69 \pm 3.01]/\sqrt{46.5} = .25 \pm .44 = [-.19, .69]$

$RCI_4 = [2.88 \pm 2.609]/\sqrt{62} = .37 \pm .33 = [.04, .70]$

(b) Approach I $\Rightarrow$ accept @ $k = K = 4$
because Ho is neither accepted nor rejected until then.

Approach II $\Rightarrow$ construct $(1-.1)$ RCI again.

$RCI_k(1-0.1) = [Z_k \pm 1.733\sqrt{4/k}\,]/\sqrt{15.5k}$:

$RCI_1 = [2.39 \pm 3.47]/\sqrt{15.5} = .61 \pm .88 = [-.27, 1.49]$

$RCI_2 = [1.33 \pm 2.45]/\sqrt{31} = .24 \pm .44 = [-.20, .68]$

$RCI_3 = [1.69 \pm 2.00]/\sqrt{46.5} = .25 \pm .29 = [-.04, .54]$

$RCI_4 = [2.88 \pm 1.73]/\sqrt{62} = .37 \pm .22 = [+.15, .59]$

$0 \notin RCI_4(1-\alpha) \Rightarrow$ reject Ho @ $k = 4$

By the way, the parent OBF test also rejects Ho @ $\alpha = 0.01$ @ $k = 4$.

OBF RCI are wider than Pocock-based ones, because OBF requires a smaller group size. However, the same Z-statistics are more extreme in this test if they are computed from smaller samples.

(3) $H_0: \mu_A = \mu_B$ vs $H_A: \mu_A > \mu_B$.

Approach I:

Compute $\xi = \dfrac{2 Z_{.99}}{Z_{.99} + Z_{.9}} = \dfrac{2(2.33)}{2.33 + 1.28} = \underline{1.29}$

So, we design a test with power $1-\alpha = .99$ @ $\tilde{\delta} = \xi\delta$
It will have power $.9$ @ $\delta = .5$. $\quad = .645$

Sample in groups of $m = \left\lceil \left(\dfrac{2C_p(.02)\sigma\sqrt{2}}{\tilde{\delta}} \right)^2 / K \right\rceil$
$= \lceil 4.8\, C_p^2(.02) \rceil \approx \underline{38}$
(we don't have $C_p(.02)$ but it is between 2.361 and 2.939)
We then construct $(1-0.02)$ RCI which are a little smaller than $(1-0.01)$ RCI in #1a.
If $\overline{\theta}_k < \tilde{\delta} = .645 \Rightarrow$ accept H_0.
If $\underline{\theta}_k > 0 \Rightarrow$ reject H_0.
Based on $(1-.01)$ RCI in #1a, we would have accepted H_0 @ $k=3$.

Approach II

$$\underline{\theta}_k^{(\alpha)} = \frac{Z_k - C_p(0.02)}{\sqrt{I_k}} \approx \frac{Z_k - 2.8}{\sqrt{mk/2}}$$

$$\overline{\theta}_k^{(\beta)} = \frac{Z_k + C_p(0.2)}{\sqrt{I_k}} \approx \frac{Z_k + 1.7}{\sqrt{mk/2}}$$

For $|\overline{\theta}_K^{(\beta)} - \underline{\theta}_K^{(\alpha)}| \approx \dfrac{4.5}{\sqrt{mK/2}} < 0.5$, need $m \geq \underline{41}$

Then accept H_0 if $\dfrac{Z_k + 1.7}{\sqrt{20.5k}} < 0.5$

reject H_0 if $\dfrac{Z_k - 2.8}{\sqrt{20.5k}} > 0$.

The observed z-statistics in #1 would yield
$\underline{\theta}_k^{(\alpha)} = -.09, -.23, -.14, +.01$; $\overline{\theta}_k^{(\beta)} = .90, .47, .43, .51$.
So, we would have $\underline{\text{rejected}}$ H_0 @ $k=4$.

④ Parent test = O'Brien-Fleming

Approach I – design a test with $\alpha = 0.01$ and power $1-\alpha = 0.99$ @ $\theta = \tilde{\delta} = 0.645$ (as in #3).

For this, we need $C_{OBF}(2\alpha) = C_{OBF}(0.02) \approx 2.5$.

Then the group size is

$$m = \left\lceil \left(\frac{2\, C_{OBF}(.02)\sqrt{K/K}\,\sigma\sqrt{2}}{\tilde{\delta}} \right)^2 \Big/ K \right\rceil = \left\lceil \frac{8\, C^2_{OBF}(.02)}{4(.645)^2} \right\rceil = 31$$

(need fewer patients than the Pocock-based test).

Construct $(1-0.02)$ RCI $\approx \dfrac{Z_k \pm 2.5\sqrt{4/k}}{\sqrt{mk/2}} = \dfrac{Z_k \pm 5/\sqrt{k}}{\sqrt{15.5k}}$

$RCI_1 = [2.39 \pm 5.00]/\sqrt{15.5} = .61 \pm 1.27 = [-.66, 1.88]$

$RCI_2 = [1.33 \pm 3.54]/\sqrt{31} = .24 \pm .64 = [-.40, .88]$

$RCI_3 = [1.69 \pm 2.89]/\sqrt{46.5} = .25 \pm .42 = [-.17, .67]$

$RCI_4 = [2.88 \pm 2.50]/\sqrt{62} = .37 \pm .32 = [.05, .69]$

If $\bar{\theta}_k < .645$ ⇒ accept H_0

If $\underline{\theta}_k > 0$ ⇒ reject H_0 ⇒ Reject H_0 @ $k=4$.

Approach II

$$\underline{\theta}_k^{(\alpha)} = \frac{Z_k - C_{OBF}(.02)\sqrt{4/k}}{\sqrt{I_k}} \approx \frac{Z_k - 5/\sqrt{k}}{\sqrt{mk/2}}$$

$$\bar{\theta}_k^{(\beta)} = \frac{Z_k + C_{OBF}(.2)\sqrt{4/k}}{\sqrt{I_k}} \approx \frac{Z_k + 2.7/\sqrt{k}}{\sqrt{mk/2}}$$

For $|\bar{\theta}_K^{(\beta)} - \bar{\theta}_K^{(\alpha)}| \approx \dfrac{7.7/\sqrt{K}}{\sqrt{mK/2}} = \dfrac{2.72}{\sqrt{m}} < 0.5$, need $m \geq 30$

(fewer than for the Pocock test).

Then accept H_0 if $\dfrac{Z_k + 2.7/\sqrt{k}}{\sqrt{15k}} < 0.5$

reject H_0 if $\dfrac{Z_k - 5/\sqrt{k}}{\sqrt{15k}} > 0$.

Based on the data in #1,

$\underline{\theta}_k^{(\alpha)} = -.67, -.40, -.18, .05$; $\bar{\theta}_k^{(\beta)} = 1.31, .59, .48, .55$.

accept H_0 @ $k=3$!

(5) Now test $H_0: \mu_A = \mu_B$ vs $H_A: \mu_A < \mu_B$, attaining significance level $\alpha = .01$ and power $1-\beta = 0.9$ @ $\theta = -0.5$.

Need the same group size 38 for approach I or $m = 41$ for Approach II.

Use $\tilde{\delta} = -0.645$ instead of $\tilde{\delta} = 0.645$.

Approach I : if $\underline{\theta}_k < -0.645 \Rightarrow$ reject H_0
if $\overline{\theta}_k > 0 \Rightarrow$ accept H_0

Based on the given data, accept H_0 @ $k = 1$.

Approach II :

We now construct $\overline{\theta}_k^{(\alpha)} \approx \dfrac{Z_k + 2.8}{\sqrt{20.5k}}$, $\underline{\theta}_k^{(\beta)} = \dfrac{Z_k - 1.7}{\sqrt{20.5k}}$

Need the same group size, $m \geq 41$.

Accept H_0 if $\dfrac{Z_k - 1.7}{\sqrt{20.5k}} > -0.5$

Reject H_0 if $\dfrac{Z_k + 2.8}{\sqrt{20.5k}} < 0$

Based on the given data,

$\overline{\theta}_k^{(\alpha)} \approx 1.15, .65, .57, .63$; $\underline{\theta}_k^{(\beta)} \approx .15$, ...

Accept H_0 @ $k = 1$.

Certainly, positive Z-statistics cannot reject $H_0: \theta = 0$ in favor of the left-tail $H_A: \theta < 0$.

So, H_0 is accepted rather early.

STAT 6390 HOMEWORK 5

Sequential Methods in Clinical Trials

(6) $\xi = \dfrac{2\phi^{-1}(.95)}{\phi^{-1}(.95)+\phi^{-1}(.90)} = 1.12 \quad \Rightarrow$ let $\tilde{\delta} = \xi\delta = 1.12 \cdot 0.5 = \underline{0.56}$.

Then, Pocock with $\alpha = \beta = 0.05 \cdot 2 = 0.10$:

Reject if $|Z_k| > 1.992$, $k \leq 3$.

$n_f = \left(\phi^{-1}(.95) + \phi^{-1}(.95)\right)^2 \dfrac{\sigma^2}{\tilde{\delta}^2} = \left(3.29 \cdot \dfrac{1}{.56}\right)^2 = 34.51$

$\Rightarrow n_K = n_f R = (34.51)(1.166) = 40.24$

$\Rightarrow$ group size $m = \lceil n_K/3 \rceil = \boxed{14}$

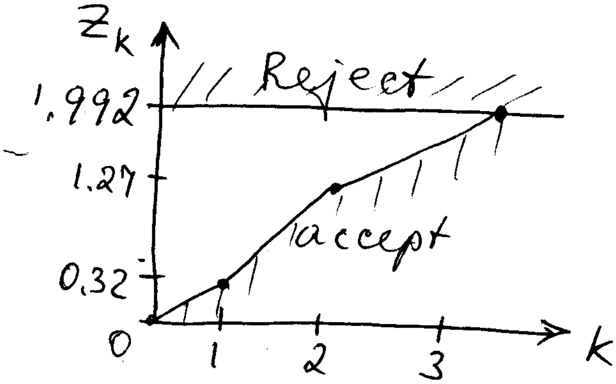
$RCI_k := \dfrac{Z_k}{\sqrt{I_k}} \pm \dfrac{1.992}{\sqrt{I_k}}$ where $I_k = Var^{-1}\bar{X}_k = \dfrac{n_k}{\sigma^2} = n_k$

Then, $RCI_k = \dfrac{Z_k \pm 1.992}{\sqrt{n_k}}$.

$$\begin{cases} \text{Accept } H_0 \text{ if } \dfrac{Z_k + 1.992}{\sqrt{n_k}} < 0.56 \Rightarrow Z_k < 0.56\sqrt{n_k} - 1.992 \\ \qquad (0.32;\ 1.27;\ 2.01) \\ \text{Reject } H_0 \text{ if } \dfrac{Z_k - 1.992}{\sqrt{n_k}} > 0 \Rightarrow Z_k > 1.992 \end{cases}$$

To terminate @ $K=3$, need

$m \geq \left\lceil \left(\dfrac{2 \cdot 1.992 \cdot 1}{0.56}\right)^2 / 3 \right\rceil = \boxed{17}$ = group size.



(7) $p_1(0) = P(S_8 \geq 7 \text{ or } S_{12} \geq 10 \mid S_4 = 0)$

$= P(S_4 \geq 7 \text{ or } S_8 \geq 10) = 0$

$p_1(1) = P(S_4 \geq 6 \text{ or } S_8 \geq 9) = 0$

$\Rightarrow$ If $S_4 \leq 1$, acceptance of H_0 is <u>inevitable</u>!

$p_1(2) = P(S_4 \geq 5 \text{ or } S_8 \geq 8) = P(S_8 = 8) = \theta^8$

$p_1(3) = P(S_4 = 4) + P(S_4 = 3, S_8 = 7) = \theta^4 + 4\theta^3(1-\theta)\theta^4$

For $\theta = 0.5$, $p_1(2) = \frac{1}{256} < \gamma$, $p_1(3) = .078 < \gamma$.

For $\theta = 0.6$, $p_1(2) = .6^8 = \underline{.017 < 1-\gamma'}$,

but $p_1(3) = .6^4 + 4(.6)^7(.4) = .174 > 1-\gamma'$

after 1 group, reject if $S_4 = 4$;
accept if $S_4 \leq 1$ (deterministic), if $S_4 \leq 2$ (stochastic).

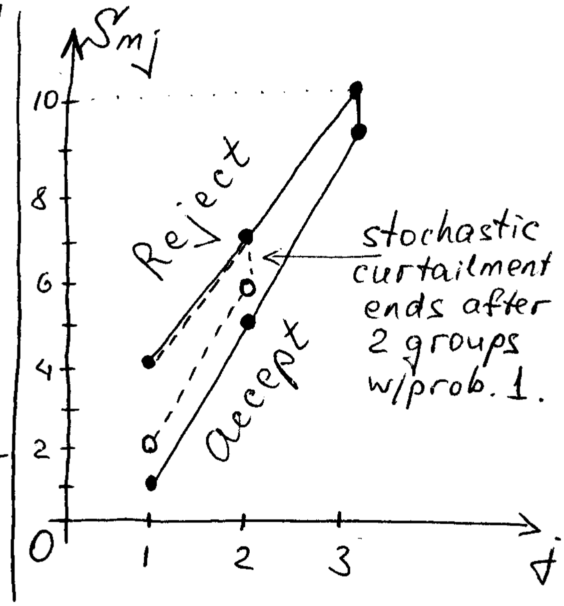
$p_2(x) = 0$ for any $x \leq 5$ and $p_2(x) = 1$ for $x \geq 7$.

$p_2(6) = P(S_{12} \geq 10 \mid S_8 = 6) = \theta^4$

For $\theta = .5$, $p_2(6) < \gamma$

For $\theta = .6$, $p_2(6) = \underline{.1296 < 1-\gamma'}$

after 2 groups, reject if $S_8 \geq 7$,
accept if $S_8 \leq 5$ (deterministic),
$S_8 \leq 6$ (stochastic)



$p_3(x) = 0$, $x \leq 9$

$p_3(x) = 1$, $x \geq 10$.

1, 2 – see ## 5, 6 of H/W 4.